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PROTEIN METABOLISM OF THE BRAIN*

BY

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Protein Metabolism During Growth

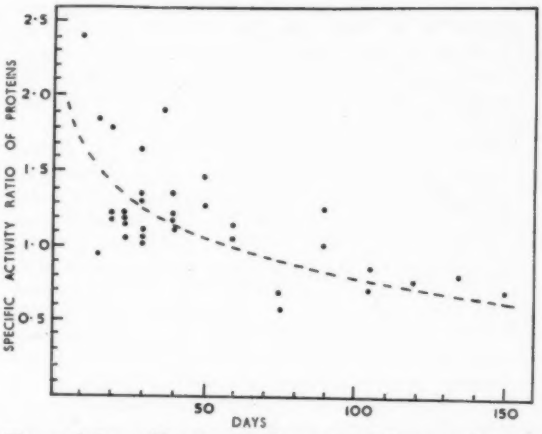
Growth involves the synthesis of the proteins and lipoproteins, which together make up some 90% of the dry weight of the brain. The growth of the brain proceeds ahead of most of the other organs of the body, since it is needed relatively early in life as a controlling centre for the neuro-endocrine functions of the body, and in the embryo of five days the brain accounts for as much as 30% of the total body weight. The activity of the enzyme systems concerned in protein synthesis is indicated by measurements of the rate of incorporation of amino-acids labelled with radioactive isotopes. Protein formation in the 13-day embryo, as indicated by the uptake of ^{14}C-glycine, is about twice as fast in brain as in liver tissue (Greenberg *et al.*, 1948). The relatively high rate of protein synthesis in the brain gradually recedes until the rate in the brain is similar to that in other tissues, and in the adult animal the rate of incorporation of amino-acids in isolated brain tissue is intermediate between that of heart muscle and liver.

The synthesis of new protein continues during the first few years of life at a rate corresponding to the rapid increase in size and weight of the brain. The water content of the foetal brain is higher than that of the adult, and on a wet-weight basis the protein concentration in the tissue shows a gradual increase throughout life; but the course of this change is not even, and there are fluctuations in the protein content corresponding to the morphological changes occurring in different parts of the brain as they become functionally active. The protein concentration is higher at first in the medulla and hypothalamus, which are also the first regions to mature: it increases later in the cerebral cortex and cerebellum, which are phylogenetically newer and the last to become functionally active.

The experiments in which the rate of incorporation of labelled amino-acids into isolated tissue was measured *in vitro* have been extended by measuring the rate of incorporation into the proteins of the brain *in vivo* of amino-acids introduced directly into the cerebrospinal fluid (Gaitonde and Richter, 1956). The rate of amino-acid incorporation is considerably higher in the newborn animal than in the adult, and there is a gradual falling off in the rate with increasing age (Chart).

The changes occurring during the growth and maturation of the brain include changes in the cell population of the tissue. In the earlier stages of development the brain tissue is made up largely of immature nerve cells, and these are the first cells to appear in considerable numbers in the mature form. The neurones reach their maximum numbers relatively early (in the human species before birth), and they are soon outnumbered by the cells of other types, which eventually make up 90% or more of the total number present in the brain. With a composite tissue of this kind considerable changes with age are to be expected in the biochemical as well as in the morphological characteristics of the tissue. Changes in enzymic activity with age have been reported by a number of investigators, and Flexner (1951–2) has related the enzymic changes to the morphological changes occurring during maturation. He has shown that there are striking changes in enzymic activity at a "critical period" during which the nerve cells become functionally mature.

Many enzyme systems, such as those concerned in the synthesis of cholesterol, disappear with the cessation of growth, and they are found to be absent or hardly detectable in the adult brain. This is true for certain enzymes related to the protein metabolism. Thus brain homogenates from the 1-day-old rat will incorporate ^{14}C from ^{14}C-labelled glucose into amino-acids, including essential amino-acids such as cystine, lysine, and histidine (Winzler *et al.*, 1952); but in homogenates from adult brain this property is missing, and the isotope is incorporated only into amino-acids such as glutamic and aspartic acids, which occupy a special position in view of their relation to the citric acid cycle.



The variation with age in the rate of incorporation of ^{35}S-methionine into the proteins of the rat brain.

*Lecture delivered at the Institute of Neurology, National Hospital, Queen Square, London, on October 6, 1958.

As development proceeds, successive changes in the activities of the individual enzymes take place. New enzymes appear, increase in activity, and later decline. The changes in metabolism may be considered in terms of ascending and descending curves of enzymic activity, which effect a gradual change from one metabolic pattern to another as the "metabolism of growth" is replaced by that of the mature cells in the functionally active centres of the brain. At first the brain functions mainly as a controlling centre in regulating the relatively slow and diffuse humoral mechanisms of the neuro-endocrine system. As the higher centres mature, the brain assumes other functions in which speed of action is of primary importance, and it becomes a centre for the rapid analysis of sensory data and the computation required for adaptive behaviour at the adult level. For this purpose it elaborates a system of neurones with large myelinated high-speed axons; and metabolism is therefore adapted to the synthesis of the special proteolipids and other complex substances needed for the laying down of myelin.

Effect of Environmental Factors on Protein Metabolism and Growth

The proteins of the brain are more resistant in general than those of other organs to depletion under conditions of starvation; but a severe protein deficiency in the mother can lead to the death or deformation of a foetus, and it is likely that a faulty environment is the cause of the changes that are seen, for example, in the small "ill-finished" brain of the mongol child. The effects of prolonged protein deficiency on the brain during the early formative years of life are indicated by the mental symptoms of apathy and deep depression that appear in kwashiorkor. Mental symptoms have also been produced experimentally by the deliberate omission of a single essential amino-acid, such as methionine or lysine, from the diet (Rose *et al.*, 1950): the symptoms of nervous irritability and fatigue quickly disappear if the missing amino-acid is restored to the diet, with or without the knowledge of the subject.

Protein formation is controlled by the growth hormone of the anterior hypophysis and it is influenced particularly by the levels of cortisone and thyroid hormone. Thyroid hormone has little effect on the metabolism of the adult brain, owing perhaps to the protective action of the blood-brain barrier in preventing the entry of the hormone into the brain; but it is needed for the functional maturation of the brain in the infant, and in the young developing animal it not only increases the rate of oxygen consumption but it also increases the overall protein content of the brain (Reiss *et al.*, 1956). The precise way in which the thyroid hormone acts is not yet clear, but it has recently been shown that the enzymes succinic dehydrogenase and cholinesterase fail to develop in the cerebral cortex if an adequate level of thyroid hormone is not present (Hamburgh and Flexner, 1957).

The normal development of the nerve cells appears to depend on their receiving a sufficient amount of physiological stimulation during growth. This has been shown very convincingly in some recent experiments of Brattgård (1952), in which he compared the retinal ganglion cells of the normal rabbit with those of animals born and reared in darkness. In animals kept for ten weeks in darkness the retinal neurones failed to develop, and the content of protein and ribonucleoprotein was considerably reduced (see Table I). These observations may be relevant to the condition of *amentia sensoripriva*, in which mental retardation is found in children deprived of forms of sensory stimulation normal for their age.

TABLE I.—*Effect of Physiological Stimulation on Retinal Ganglion Cells of the Rabbit (Weight in* 10^{-9} *mg./*μ^3*. Brattgård,* 1952)

Treatment	Ribonucleoprotein	Proteins
Daylight 10 weeks	0·47	0·31
Darkness ,, ...	0·0	0·16

The conditions required for the optimal growth and development of the brain during the foetal and post-natal periods are not yet clearly understood, but it would appear that environmental factors affecting the protein metabolism may be concerned in the causation of some of the neurological conditions, such as certain forms of cerebral palsy, in which the neurones fail to develop normally.

Proteins of the Brain

What is the nature of the proteins that are normally present in the brain? The earlier investigators were able to separate only five or six proteins from brain tissue. These include albumin, globulin, phosphoprotein, and nucleoprotein, which could be extracted in aqueous solution, and the insoluble proteins collagen, reticulin, and "neurokeratin": but none of these proteins was obtained pure and only one, neurokeratin, could be regarded as in any way characteristic of nervous tissue. Neurokeratin was obtained mainly from the white matter of the brain by treatment with strong acid followed by prolonged digestion with proteolytic enzymes, but it does not have the amino-acid content typical of a true keratin, and the neurokeratin prepared in this way would appear to be an artifact derived mainly from the inositol-containing proteolipids through the action of the drastic reagents used in its preparation (LeBaron and Folch, 1956). It has recently been confirmed that the neurokeratin described by histologists as a structural component of the myelin sheath also has the properties of a proteolipid (Koenig, 1959). Collagen and elastin are present in significant amounts in the connective-tissue sheath of peripheral nerve, but in brain tissue they are present only in very small amounts (about 0.2% of the normal protein content), which suggests that they may be derived from the blood vessels and not from the neurones or glial cells.

Recent work has added greatly to the number of proteins known to be present in nervous tissue. Up to 10 proteins have now been separated by electrophoresis from the soluble cytoplasmic fraction of the brain proteins (Robertson, 1957), and the proteins of the cell nuclei, mitochondria, and microsomes, have been fractionated in various ways (Clouet and Richter, 1959; Robertson, 1959). By the use of milder methods of extraction it has been possible to isolate in various degrees of purity a liponucleoprotein (Folch and Uzman, 1948), three copper-containing proteins—cerebrocuprein I, II, and III (Porter and Folch, 1957)—three proteolipids (Folch and Lees, 1957), the physiologically active van Dyke protein of the hypophysis, and a number of different enzymes, including cholinesterase.

It used to be believed that tissues such as brain were made up largely of structural proteins and that the quantity of enzymes present was relatively small; but it has become increasingly hard to draw a distinction between the proteins with enzymic activity and those with a structural role. Besides the enzymes in the soluble phase, certain enzymes are now known to be closely associated with structures such the the mito-

chondrial membranes, with the microsomes, and even with the myelin sheath (Schmitt, 1957). There is reason to believe that, as in muscle and other tissues, enzymes may make up the main bulk of the proteins in the cells of the living brain. The number of enzymes hitherto identified in nervous tissues runs into a considerable figure, but it is likely to form only a small fraction of the total number that are present, and if every enzyme is regarded as a separate protein entity the total number of proteins must be very large. Estimates based on the number of genes in the organism, assuming the presence of one enzyme for every gene, lead to figures of the order of more than 20,000 for man.

The proteins of the brain are not the same as those in peripheral nerve, and the protein distribution varies in different parts of the brain. This is shown by studies of the distribution of enzymes, some of which are present in higher concentration in the grey matter than in the white. Differences have also been shown in the proteins in different topographical regions. Thus the enzyme cholinesterase is present in relatively high concentration in the caudate nucleus. Differences have been found again in the distribution of the soluble proteins separated by electrophoretic methods: the proteins in the cerebral cortex differ significantly from those in the hypothalamus and other regions of the brain (Robertson, 1959).

Protein Changes in Pathological Conditions

Gross changes in protein structure are recognized in many "organic" conditions, and they are shown very well by the classical histological staining techniques, which are mainly designed for demonstrating proteins. These methods have also led to the recognition of protein changes of a milder kind associated with less drastic forms of injury to the nerve cells. Of particular interest are the characteristic changes known as "chromatolysis," in which there is a dissolution of the liponucleoprotein aggregates constituting the Nissl granules in fixed preparations. This is not a simple proteolysis, for the proteolytic enzymes of nervous tissues do not act directly on nucleoproteins. There is evidence that the dissolution of the Nissl granules during chromatolysis is due to the action of a ribonuclease which first splits up the large ribonucleic acid residues (Gersh and Bodian, 1943). Other concomitant changes, such as the swelling of the nerve cell bodies and dilution of the cell contents, are attributable to the increase in osmotic pressure in the cytoplasm due to the liberation of smaller nucleotide molecules and protein fragments as proteolysis ensues. Chromatolysis is an unspecific reaction of the nerve cell to an injury of any kind, and it is seen in many different pathological conditions. In the recovery process there is an active synthesis of new protein in the nerve cell bodies, and protein passes out into the axoplasm.

Very little is known about the distribution of soluble proteins in the brain in pathological conditions, but preliminary investigations by electrophoretic methods have shown that there is an abnormal distribution, with a relative increase in the slow-moving "γ-globulin" fraction in the brains of patients with subacute sclerosing leucoencephalitis (Karcher *et al.*, 1959). Electrophoretic studies of the proteins present in oedematous areas of the brain have shown a relative increase in the fast-moving albumin and α-globulin fractions: this has been found, for example, in the oedematous areas adjacent to cerebral tumours and other lesions of the brain. It is known that the proportion of fast-moving proteins is higher in the immature infant brain than in the adult, and it has been reported that they are also present in abnormal amounts in patients suffering from certain forms of epilepsy (Kiyota, 1957). It has been suggested by Kiyota (1957) that these fast-moving proteins are highly hydrophilic and so may account for the higher water content and the greater tendency to cerebral oedema, and hence to convulsions in infants and in epileptics. The proteins of the infant brain contain a higher arginine/histidine ratio than those of the adult, and in this connexion it may be relevant that an abnormally high arginine/histidine ratio has been found in the proteins of the brain of a patient suffering from late amaurotic familial idiocy (Block, 1937). The presence of an abnormal form of copper protein has been reported in the brains of patients with Wilson's disease (Porter, 1959).

Brain tissue contains a powerful cathepsin which is about 12 times more active than that in muscle. This enzyme may be expected to act as a transpeptidase under normal physiological conditions, but it may act as a proteolytic enzyme and cause the breakdown of proteins under pathological conditions. Brain tissue also contains a "neutral proteinase" which can break down proteins at the neutral *p*H (Ansell and Richter, 1954). It has recently been reported that this enzyme, or a similar proteolytic enzyme, is released from the brain into the cerebrospinal fluid in patients suffering from migraine and other active neurological conditions (Chapman and Wolff, 1958). Chapman and Wolff (1958) have suggested that the polypeptides formed through the action of this enzyme may play a part in stimulating the pain nerve endings and in causing the vascular changes associated with attacks of migraine.

In view of the large number of enzymes that are believed to be present, the scope for individual variation in enzymic activity is clearly very great, and it is hardly surprising if it occasionally happens that, for genetic or other reasons, a particular enzyme is missing or deficient in the cell. A number of pathological conditions are now recognized in which the metabolism of the brain is affected by metabolic errors of this kind. They include such well-known examples as phenylketonuria, in which there is a congenital inability to hydroxylate phenylalanine, and the congenital lipidoses or "storage" diseases. An abnormal distribution of enzymes in the brain has been reported in patients suffering from vascular disorders of the brain, and it has been suggested that a faulty distribution or imbalance of enzymes might account for some of the changes occurring in psychotic conditions (Richter, 1957).

Protein Metabolism of the Adult Brain

Analyses of the blood entering and leaving the brain have shown that there is an active utilization of glucose, but practically no utilization of the amino-acids in the blood traversing the brain. There is also very little uptake of labelled amino-acids such as ^{14}C-tyrosine *in vivo* by the brain. These observations led to the view that the proteins of the brain are metabolically inactive: but more recent work has shown that the low uptake of labelled amino-acids into the brain is largely attributable to the blood-brain barrier, and there is an active incorporation of amino-acids if the blood-brain barrier is bypassed by introducing them direct into the cerebrospinal fluid (Gaitonde and Richter, 1956). Calculations of the mean half-life of the proteins during a period of 20–60 minutes' incorporation of ^{35}S-

methionine indicated a mean half-life of 14 days. Since it is known that the proteins of the brain are not homogenous it is clear that some of the proteins will have a longer and others a shorter half-life, but the estimate of 14 days may be compared with other estimates of 6 days for the proteins of the visceral organs and up to 50 days for the carcass proteins of the rat. Figures ranging from 6.2 to 15.2 (mean 10.7) days have recently been reported for the half-life of the mixed protein of the mouse brain determined for a similar period by means of ^{14}C-lysine (Waelsch, 1957). Such estimates for mixed proteins tell us nothing about the rates of incorporation into individual protein fractions, and they are also subject to error, since they assume a uniform amino-acid "pool" in the brain and ignore the fact that the specific activity of the amino-acids must differ in the different cell compartments in the brain.

More recent measurements of the rate of uptake of labelled amino-acids into isolated cell particles obtained from brain tissue by differential centrifugation have shown a relatively high rate of incorporation in the proteins of the microsomes, while the uptake into the proteins of the cell nuclei, mitochondria, and supernatant fraction is relatively slow (Clouet and Richter, 1959). The protein showing the highest rate of incorporation is a liponucleoprotein corresponding to the Nissl granules: it can be extracted from the microsomes by means of dilute alkali, and contains approximately equal amounts of lipid and protein and 3.8 g. nucleic acid per 100 g. of protein. Estimates of the half-life of this liponucleoprotein based on the rate of incorporation of ^{35}S-methionine and on the shape of the specific activity–time curve have given figures of the order of 50–100 minutes for the half-life of this protein (Clouet and Richter, 1959). The proteins of the nuclei, mitochondria, and soluble fractions give considerably longer half-lives: the rate of incorporation of amino-acids into the white matter of the brain, and into the proteolipids, which are a major constituent of the white matter, is relatively slow.

The rate of incorporation of amino-acids varies in different parts of the brain. This has been shown in experiments by an autoradiographic method in which the distribution of radioactivity in the tissue was studied after administering ^{35}S-methionine to animals *in vivo* by the intracisternal and intraperitoneal routes (Cohn *et al.*, 1954). It was found that the uptake of ^{35}S-methionine was considerably greater in the grey matter than in the white matter of the brain. In the brains of 1-day-old rats the incorporation was relatively diffuse, but was more pronounced in the cerebral cortex than in the regions mainly containing nerve fibres. In older animals the incorporation was most active in the cellular layers containing a high proportion of nerve cell bodies. There was a marked incorporation in the cerebellum, in the cerebral cortex, and in the *pyramidalis* layer of Ammon's horn. The highest rate of incorporation was in the supraoptic nucleus and other hypothalamic nuclei containing neurosecretory cells. These observations have been confirmed by direct measurements of the radioactivity of regions of the brain removed by dissection after the administration of a labelled amino-acid (Cohn *et al.*, 1959).

The rate of amino-acid incorporation *in vivo* is decreased in narcosis with sodium pentobarbitone or ether, and there is a marked decrease if the temperature is allowed to fall. There is also a decrease of about 25% in the amino-acid incorporation during insulin coma, but electrical stimulation of the brain does not greatly affect the amino-acid incorporation.

TABLE II.—*Amino-acid Turnover of Proteins of the Rat Brain in vivo after administering ^{35}S-methionine by Intracisternal Injection (Gaitonde and Richter, 1956)*

	Specific Activity Ratio	Change %	P
Normal	99	—	—
Ether	65	−34	0·02
Pentobarbitone	75	−24	0·001
Reduced temp.	29	−70	0·001
Insulin hypoglyc. ..	75	−24	0·003
Stimulation	80	−19	0·001

Besides the incorporation of amino-acids there are a number of other reactions in which the proteins of the brain are known to take part. It has recently been shown that there is a reversible uptake and release of ammonia from the amide groups of the glutamine residues in the brain proteins (Vrba, 1956). This reaction is of particular interest, since there is evidence that functional activity is associated with the liberation of free ammonia in the brain, and it has been shown that changes can be produced in the amide nitrogen content of the brain proteins of the rat during prolonged neuromuscular activity. The tissue proteins have also been shown to combine with various pharmacologically active amines, and the uptake has been measured by the use of the labelled metabolites ^{14}C-mescaline and ^{14}C-β-phenylethylamine (Block, 1954; Clarke *et al.*, 1957).

Further evidence of the metabolic activity of the proteins of the brain *in vivo* has been obtained in studies of the uptake of labelled phosphate into a phosphoprotein that is present in the brain. It has been shown that the phosphate in these phosphoproteins is combined in the hydroxyl groups of the serine units: the rate of turnover is influenced by a number of factors including electrical stimulation of the tissue (Heald, 1958). Evidence has been obtained that electrical stimulation of the brain under certain conditions can cause a reversible change in the configuration of the protein molecules, which is probably attributable to a partial hydrolysis of amide bonds (Ungar *et al.*, 1957).

The reason for the active protein metabolism in the brain has been a subject for considerable speculation. It is known that under special conditions, where there is a deficiency of glucose, the brain is able to utilize protein as an alternative source of energy, and recent work has suggested that the metabolism of functionally active neurones differs from the resting metabolism in that there is a preferential utilization of amino-acids. Thus, stimulated nerve differs from resting nerve in showing a preferential utilization of glycine, alanine, and glutamic acid (Mullins, 1953) (Table III). The active synthesis of protein in the neurosecretory cells of the hypothalamus is now well established, and these observations suggest that there may be an active utilization of protein associated with functional activity in other parts of the brain.

TABLE III.—*Utilization of Substrates by Stimulated Nerve (Mullins, 1953)*

	Increase % in CO_2 over Resting Metabolism		Increase % in CO_2 over Resting Metabolism
Glucose ..	−22	Glycine	50
Acetate ..	−51	Alanine	80
Pyruvate ..	0	Glutamate ..	140
Lactate	0		

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TRIAMCINOLONE IN THE TREATMENT OF RHEUMATOID ARTHRITIS

BY

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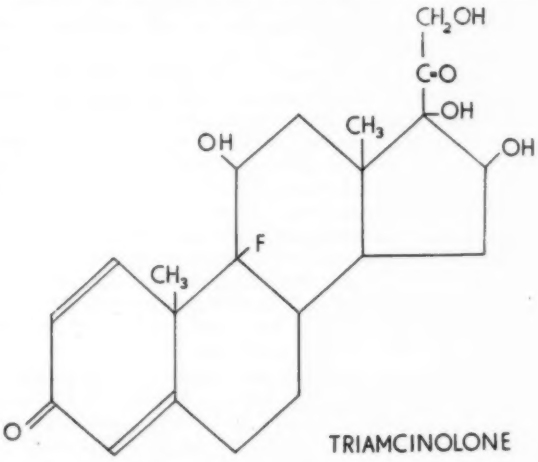
Triamcinolone is a synthetic steroid, being the 9α-fluoro-16α-hydroxy analogue of prednisolone (see Formula). It has been shown to possess powerful anti-inflammatory properties with minimal mineralo-corticoid activity. Bernstein *et al.* (1956) reported that, by rat-liver glycogen assay, triamcinolone was 18 to 36 times as potent as hydrocortisone, and in the adrenalectomized rat it did not produce any sodium retention. Hellman *et al.* (1957) described its clinical and metabolic effects, and demonstrated that it had excellent anti-inflammatory properties with, in ordinary therapeutic dosage, little or no effect upon nitrogen, calcium, potassium, or sodium balance. Assessment of the anti-inflammatory effects of triamcinolone suggested that it was more powerful than prednisolone in an approximate ratio of 4:3 when administered orally.

Sherwood and Cooke (1957) described the results of treatment of 26 patients suffering from allergic conditions, chiefly asthma or dermatitis, and thought that an equal weight of triamcinolone was about twice as potent as prednisone or prednisolone. Rein *et al.* (1957) also reported upon the use of triamcinolone in dermatological cases, and concluded that an equivalent therapeutic effect was produced by a dosage between one-half and two-thirds of that of prednisolone. Shelley *et al.* (1958) considered that triamcinolone had a significant suppressive effect on psoriasis in 60% of their 60 cases, but that the relapse which invariably followed cessation of treatment limited its value.



TRIAMCINOLONE

Hartung (1958) reported favourably on the use of triamcinolone in 67 patients suffering from rheumatoid arthritis, and stated that it possessed several advantages over other steroids, including fewer gastro-intestinal symptoms. Dubois (1958) treated 31 cases of disseminated lupus erythematosus with triamcinolone, and his experience suggested that this new steroid did not precipitate gastro-duodenal symptoms or lesions. Hart *et al.* (1958) did not find any evidence that triamcinolone either aggravated or reduced gastro-duodenal side-effects in their series of 25 rheumatoid patients, all of whom had received previous treatment with prednisolone.

Since the demonstration by Bunim *et al.* (1955) that the △-1- or predni- analogues possessed four or five times the anti-inflammatory activity of cortisone and hydrocortisone, with much fewer sodium-retaining effects, there have been further attempts to find even more powerful steroid compounds. The mere anti-inflammatory potency of a steroid compound is not, of itself, important in assessing the value of the drug as a therapeutic agent, as a less potent steroid could be administered in larger dosage provided this did not produce undesirable side-effects. It is largely on the basis of side-effects, therefore, that a new steroid is to be evaluated. The lessening or elimination of mineralo-corticoid effects, especially hypertension and hypopotassaemia, are important considerations, but other side-effects to be considered are peptic ulceration, mental disturbance, osteoporosis, lowered glucose tolerance, purpura, telangiectasia, and subcutaneous haemorrhages, facial mooning and flushing, and acne and hirsuties.

The purposes of the present investigation were to determine (*a*) whether triamcinolone was as effective or better than prednisolone when administered in a dosage not exceeding four-fifths of the prednisolone dosage; (*b*) whether triamcinolone warranted a place for selected, or indeed all, patients for whom systemic

steroid therapy was considered advisable; (*c*) whether, on the basis of a short-term trial, side-effects appeared to be qualitatively or quantitatively different from those seen with prednisone or cortisone; and (*d*) whether triamcinolone could be used as an immediate substitute for prednisolone or cortisone in the event of side-effects arising with the latter drugs.

Method of the Trial

Of the 16 patients concerned, 15 were suffering from rheumatoid arthritis and one from ankylosing spondylitis with predominantly peripheral arthritis. All received treatment successively with prednisolone and triamcinolone, the ratio of dosage being 5:4 by weight. The daily maintenance dosage of prednisolone ranged from 7.5 to 20 mg. The duration of treatment with triamcinolone varied from 2 to 26 weeks, and 11 of the patients were then given a further course of treatment with prednisolone, allowing a second comparison to be made. The patients had become accustomed to receiving steroid tablets of different sizes from different manufacturers, and they were not informed that any change in treatment had been made, so that any bias in favour of a new treatment was avoided.

Response to treatment was judged by the patient's own assessment of pain and the duration of morning stiffness, in addition to the physician's assessments of functional capacity and disease activity. Alterations in the number of joints affected were noted, and blood pressure, weight, and strength of grip were recorded. Grip was tested at weekly intervals by recording the height in millimetres of mercury reached by squeezing a rubber bag 6 by 3 in. (15 by 7.5 cm.) attached to a sphygmomanometer. Three measurements of grip were made for each hand, and the average was calculated. Then the average for both hands was calculated. Serial recordings of capillary resistance, measured by the apparatus and method described by Potter and Wigzell (1957), in their first survey of capillary resistance in rheumatoid arthritis, were made in seven patients. Serial measurements of the erythrocyte sedimentation rate (Westergren method) were done at weekly or fortnightly intervals. The lowest reading obtained while the patient was receiving prednisolone was compared with the average reading recorded while the patient was receiving triamcinolone.

Results

The results are presented in Table I. Of the 16 patients, six preferred triamcinolone, five preferred prednisolone, and five had no preference. These preferences were based on the patient's own assessments of pain and stiffness, plus sense of well-being. In respect of pain, six patients preferred triamcinolone, four felt pains to be increased while on triamcinolone, and six noticed no difference. With regard to severity and duration of morning stiffness, seven patients considered this to be less while they were receiving triamcinolone, two felt it to be worse, and in seven there was no difference. Functional capacity improved significantly in three patients while receiving triamcinolone; in the remainder it was unchanged. Disease activity was significantly reduced in two patients while receiving triamcinolone, and in the remainder it was unchanged.

Measurements of the grip, by the method described above, were recorded in all cases. In view of ordinary variations in this measurement, an overall average improvement of at least 20 mm. of mercury was considered necessary to constitute significant improvement. This level was achieved in four patients during triamcinolone therapy, there being no significant increase or decrease in the remaining 12.

TABLE I.—*Results of Treatment with Triamcinolone Compared with Those of Prednisolone*

Case No.	Sex	Joint Pains	Stiffness	Functional Capacity	Disease Activity	Grip	E.S.R.		Patient's Preference
							Pred.	Triam.	
1	F	Less	Less	0	0	0	38	33	Triam.
2	M	"	"	0	0	Imp.	42	26	"
3	F	"	"	0	0	0	12	10	"
4	F	0	0	0	0	0	28	25	None
5	F	0	Less	0	0	0	4	13	"
6	F	0	0	0	0	0	20	15	"
7	F	0	0	0	0	0	6	6	"
8	F	Inc.	Inc.	0	0	0	11	14	Pred.
9	M	Less	Less	Imp.	Less	Imp.	27	12	Triam.
10	F	0	0	0	0	0	16	12	None
11	F	Less	Less	Imp.	0	Imp.	5	5	Triam.
12	F	0	0	0	0	0	28	17	Pred.
13	F	Inc.	0	0	0	0	13	12	"
14	F	"	0	0	0	0	39	45	"
15	M	"	Inc.	0	0	0	15	11	"
16	M	Less	Less	Imp.	Less	Imp.	33	15	Triam.

Comparisons of the E.S.R. during the two treatments showed it to be lower during triamcinolone therapy in 11 instances, equal in two, and lower during prednisolone therapy in three. In only two patients, however (Cases 9 and 16), was the difference at all striking, and both of these were in favour of triamcinolone. The average lowest E.S.R. recorded, for the group as a whole, during prednisolone therapy was 21 mm., compared with an average of 16.6 mm. during triamcinolone therapy.

Serial measurements of the capillary resistance in seven patients did not show any important difference, the high levels characteristic of patients receiving systemic steroid therapy being found during both treatments.

Side-Effects

The side-effects are recorded in Table II. All but two patients showed *loss of weight* while receiving triamcinolone. Of the five patients who lost 4 lb. or more, three had developed oedema of the ankles during previous steroid therapy. No significant changes in the levels of plasma sodium, potassium, or chloride were seen in any of these patients, and in no instance was there any complaint of weakness or muscular fatigue. (Case 10 was on a 1,000-calorie diet during the period of the trial and no comparison of weight was possible.) The last, and representative, *blood-pressure* readings during prednisolone therapy are compared with those obtained at the end of the period of triamcinolone therapy. Nine patients had a diastolic pressure of 90 mm. or more during prednisolone therapy; in six of them there had been no evidence of hypertension prior to steroid therapy (cortisone or prednisolone); in three instances a pre-existing hypertension had increased during steroid therapy. In all nine patients there was a fall in blood pressure during treatment with triamcinolone. This was especially so in two known hypertensive patients (Cases 2 and 3), who had shown B.P. levels of over 220 systolic and 120 diastolic on occasion during prednisolone therapy.

In respect of *dyspepsia*, it is seen that four patients who complained of dyspepsia during prednisolone therapy retained these symptoms during triamcinolone therapy and in three instances they were more severe. In addition a further four patients complained of dyspepsia for the first time during triamcinolone

therapy, and one of these had haematemesis following vomiting attacks extending over three days.

Two patients had developed *purpura* and *multiple subcutaneous ecchymoses* during prednisolone therapy, and these lesions regressed when triamcinolone was substituted. One of these (Case 3) subsequently exhibited three small areas of apparently spontaneous subcutaneous bruising, but it was at this time that her triamcinolone was discontinued, so that further observation of the progress of the lesions was not possible. *Acneiform skin lesions*, noted in two patients, remained unchanged during treatment with triamcinolone. *Facial mooning*, evident in three patients, and *hirsuties*, troublesome in one, remained unaltered during both treatments.

Two patients were noted to be *euphoric* and restless while taking prednisolone. Both were calmer and less loquacious while taking triamcinolone, and one complained of drowsiness.

One patient had developed glycosuria with a diabetic type of blood-sugar curve during prednisolone therapy. These features remained unchanged when she was given triamcinolone, a repeat blood-sugar curve after 18 weeks of triamcinolone therapy being virtually unchanged. *Flushing and sweating* were symptoms reported by two patients during triamcinolone therapy and not observed with prednisolone.

Additional Cases

In addition to the patients concerned in the trial, a further four patients have been treated with triamcinolone. Three of these were women suffering from rheumatoid arthritis, and the fourth was a man suffering from ankylosing spondylitis. The dosage was 4 mg. four times daily initially, reducing to 12 mg. total daily dose. Two of the female patients have had continuous treatment for 13 weeks without any evidence of side-effects, and one of them, who had pre-existing hypertension, has shown consistently lower blood-pressure readings since she started treatment.

The third female patient has also obtained sustained benefit during the same period, the only complication being the appearance of a crop of spontaneous ecchymoses over the ankles and shins 10 days after the starting of treatment. In the absence of any evidence of haemorrhagic complications it was decided to continue treatment, under close observation, with the same dosage of triamcinolone, 12 mg. daily. The lesions faded during the ensuing week and no new lesions appeared until 10 weeks later, when similar small crops of lesions occurred over the forearms and shins.

The fourth patient, a man aged 27, had ankylosing spondylitis with severe peripheral arthritis. He had taken large quantities of A.P.C. tablets, up to 20 daily, and calcium–aspirin tablets, with only slight dyspepsia. A barium-meal examination did not reveal any evidence of a peptic ulcer, and triamcinolone therapy was started on June 2, with a maintenance dosage of 16 mg. daily. He responded well, and within a week his E.S.R. fell from 112 to 31 mm. in one hour. After brief premonitory symptoms of nausea on July 2 he had a profuse haematemesis and was admitted to hospital immediately in a state of severe shock. He recovered with transfusions of 4 pints (2 litres) of blood, and steroid therapy was maintained, initially with intravenous hydrocortisone and subsequently with intramuscular cortisone. He has since been treated with injections of zinc-protamine corticotrophin and has remained well on a maintenance dosage of 30 units every third day, without any recurrence of gastric symptoms.

Discussion

Although the place of a new steroid preparation in the treatment of a chronic disease can be fully assessed only on long-term therapy, short-term studies do provide some useful information. It is evident that, in answer to the first question raised in the introduction, triamcinoline is as effective as prednisolone in a dosage ratio of 4:5. When any advantage occurred in changing from one drug to the other the difference was small. The findings of Sherwood and Cooke (1957) in the treatment of allergic disorders, and of Rein *et al.* (1957) with regard to skin diseases, that triamcinolone could be as effective as prednisolone in half to two-thirds the dosage, were not substantiated in this series of patients treated for rheumatoid arthritis. The maintenance dosage was found to be between 6 and 16 mg. daily according to the severity of the case.

In this trial triamcinolone did not exercise any adverse influence upon hypertension. Where hypertension had been induced (six patients) or increased (three patients) by previous steroid therapy, consistent improvement occurred on transfer to triamcinolone. Only long-term studies will determine whether this effect will be maintained or whether it may be associated with other, possibly undesirable, effects—

TABLE II.—*Side-effects of Triamcinolone Compared with those of Prednisolone*

Case No.	Sex and Age	Duration of Treatment (Weeks)	Weight Loss		Blood Pressure		Side-effects	
			lb.	g.	Pred.	Triam.	Prednisolone	Triamcinolone
1	F 51	11	1½	680	160/92	132/80	Moon face. Hirsuties. Hypertension. Mild dyspepsia	Moon face. Hirsuties. Increased dyspepsia
2	M 53	4	2½	1,134	192/116	164/106	Increased hypertension	Decreased hypertension
3	F 49	12	5½	2,495	218/104	178/90	Increased hypertension. Bruising	Less bruising. Less hypertension. Haematemesis
4	F 37	14	4½	2,040	142/92	134/82	Hypertension. Bruising and purpura	Mild dyspepsia
5	F 58	14	1½	680	160/90	134/84	Moon face. Hypertension	Moon face
6	F 67	3	4	1,815	154/94	132/82	Hypertension. Euphoria ++. Oedema of ankles	Less oedema of ankles. Less euphoria
7	F 62	6	Nil		174/100	154/86	Euphoria. Hypertension	Flushing and sweating. Slight drowsiness
8	F 60	2	1½	680	115/64	114/66	Mild dyspepsia	Mild dyspepsia. Flushing and sweating
9	M 49	3	4	1,815	128/82	124/80	Acne	Acne
10	F 53	20	On diet		140/86	122/80	Glycosuria	Glycosuria
11	F 46	15	3	1,360	140/84	134/72	Moon face	Moon face
12	F 50	2	Nil		108/69	108/66	Nil	Nil
13	F 71	3	1½	680	184/104	168/86	Mild dyspepsia. Hypertension	Dyspepsia
14	F 47	9	3	1,360	184/108	143/84	" " "	"
15	M 40	2	6	2,720	128/86	138/86	Acne	Acne. Anorexia and nausea. Dyspepsia
16	M 57	5	1	455	128/84	120/72	Nil	Mild dyspepsia

for example, sodium depletion. Loss of weight was seen in most of the patients transferred from prednisolone to triamcinolone; and oedema, when present, was diminished. No weight loss was seen in the four patients who had not received previous steroid therapy, but such weight loss has been recorded (Hellman *et al.*, 1957). At present, therefore, triamcinolone would appear to be the compound of choice when steroid therapy is indicated for patients who have hypertension or evidence of sodium retention, or who have developed these features as a result of previous steroid therapy.

Apart from hypertension and oedema, the other side-effects seen during triamcinolone therapy were very similar to those of prednisolone. Dyspepsia was more evident with triamcinolone, this finding being at variance with the experience of Hartung (1958) and Dubois (1958). The fact that, in this series, 2 out of 20 patients treated suffered haematemeses is an additional warning that triamcinolone can cause and aggravate gastro-duodenal lesions. One of these patients had previously had two years of continuous steroid therapy without dyspepsia.

In respect of other side-effects the only striking difference observed was in one patient (Case 4) who developed multiple subcutaneous ecchymoses during prednisolone therapy, which cleared rapidly on transfer to triamcinolone and have not recurred during 14 weeks of treatment. Another patient (Case 2) showed similar lesions with prednisolone which also cleared on transfer to triamcinolone but recurred slightly after 12 weeks of treatment, when triamcinolone was discontinued because of a haematemesis. Skin lesions of this type occurring during steroid therapy have been studied by Nashelsky and Smyth (1958) and appear to be particularly common with the "predni-" groups of steroids, where there is a double bond in the 1, 2 position of the steroid nucleus. Their occurrence during treatment with another predni-steroid, 6α-methyl-prednisolone, has been described by Boland and Liddle (1957). It is clear that such lesions occur also during triamcinolone therapy, as noted in two patients in the present series, but their appearance and severity in individual patients did not parallel their severity during prednisolone therapy. The clinical significance of these ecchymoses is as yet unknown; they are not apparently associated with any haemorrhagic tendency or visceral lesions, and investigations of capillary resistance have indicated raised levels in adjacent skin areas. In the event of such lesions being severe and unsightly, a change from prednisolone to triamcinolone would be indicated.

In respect of other complications—for example, glycosuria, moon face, hirsuties, facial flushing, sweating, and acne—no important difference was observed between the two groups. No observations in respect of osteoporosis could be made in this trial. In no instance did any unusual or new arthritic lesions develop, as seen by Wells (1958) during the treatment of certain non-articular diseases with triamcinolone.

When the more serious complications of steroid therapy develop there may be an urgent need to change the steroid preparation, followed when necessary by gradual withdrawal of steroid therapy altogether. On the results of this trial and others, triamcinolone would appear to be a suitable steroid compound when steroid therapy was indicated for (*a*) hypertensive patients or those who have developed hypertension with another steroid; (*b*) patients with oedema and evidence of salt retention; (*c*) patients who develop purpuric or ecchymotic lesions during treatment with other steroids; and (*d*) it may be of value for patients who have become restless or unduly euphoric on other steroids.

Modifications of the chemical structure of cortisone, including methyl-, hydroxyl-, and halogen substitution, and dehydrogenation, have produced more potent steroid compounds, with fewer undesirable side-effects. To some extent the pharmacological properties of a new steroid can be predicted from its chemical formula. It is possible that further compounds, representing almost pure anti-inflammatory substances, may become available. Certainly a steroid free from gastro-duodenal side-effects would be a valuable drug in present circumstances. However, the long-term consequences of anti-inflammatory therapy in rheumatoid arthritis are not yet known, and the place of steroid therapy in this disease is still in question. Despite the introduction of stronger and safer steroids, the maxim that "the absence of contraindications does not mean that the drug is indicated" is to be kept in mind.

Summary

The treatment of 15 patients suffering from rheumatoid arthritis and one suffering from ankylosing spondylitis was changed from prednisolone to triamcinolone for a period of 2 to 20 weeks. In addition four other patients were treated with triamcinolone. Triamcinolone was found to be as effective as prednisolone in relieving arthritic symptoms in a dosage ratio of 4 : 5. The average daily maintenance dosage of triamcinolone ranged from 6 to 16 mg., according to the severity of the disease.

Triamcinolone was found to be useful in hypertensive patients when hypertension had been induced or increased by previous steroid therapy. Weight loss and reduction of oedema were noted when patients receiving prednisolone were transferred to triamcinolone. Gastro-duodenal side-effects were more frequent and severe with triamcinolone than with prednisolone, and in the total series of 20 patients two had haematemeses while taking triamcinolone. Subcutaneous ecchymoses and other side-effects of prednisolone were also encountered with triamcinolone, but the pattern of involvement was not identical.

The value and place of triamcinolone in the treatment of rheumatoid arthritis are discussed.

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DIAGNOSIS IN THE MANAGEMENT OF BURNS*

BY

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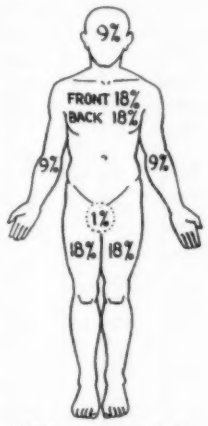
An extensive burn is an incident which starts a fast-moving progressive illness. The natural history of the disease is known. Within an hour or two a severe burn will produce oligaemia, clinical shock, and sometimes renal failure. Bacterial colonization of the burn surface follows, and sometimes invasive infection. Soon anaemia and wasting become apparent, and in a few weeks the formation of fibrous tissue may cause contractures and deformity. Against this background the need for *constant re-diagnosis* of the patient's changing condition is imperative to prevent or arrest the expected complications.

To achieve more accurate assessment a constant endeavour is being made to introduce into the early stages of emergency treatment new diagnostic methods of proved value. Although special investigations are difficult to fit into the tempo of emergency treatment—and these call for increased staff and facilities—they are part of the price of improving treatment and saving more desperate cases. Like the fast-moving traffic on the highway, the fast-moving illness of trauma can be handled most safely in a separate lane which is unobstructed by slower-moving problems.

Without doubt, the commonest mistake in the management of severe burns at present is the failure to make an adequate diagnosis. In no other branch of medicine do we so easily neglect physical signs or fail to look for them. Perhaps this is partly because so much of the skin surface is burned, and therefore untouchable by bare hands for fear of implanting infection. Again, if extensive burns are dressed, little of the patient can be examined except when they are re-dressed. Neither of these difficulties is insuperable, and I think that the chief reason for our failure to assess burned patients adequately is a genuine lack of appreciation of the importance of diagnosis. For this reason it is perhaps worth while to consider the management of severe burns in a way which will answer the question, "What should we look for, and how should we look for it?"

Diagnosis of a "Shock Case"

Most of the severely burned patients in this country reach hospital an hour or two after injury, and so the emphasis in treatment is on the prevention rather than the correction of shock. For prevention one must be able to diagnose a shock case before the complication occurs. Fortunately the plasma loss which is responsible for shock is roughly proportional to the extent of the body surface involved, and it is now established that if a burn extends over more than about 10% of the body surface in a child, or more than 15% in an adult, the patient will generally become clinically shocked after a few hours if the plasma loss is not replaced by colloid infusion. To diagnose the shock case one therefore needs to bear in mind these critical figures and some method of assessing body surface such as the "rule of nines" (see Diagram). Although the rule of nines is only a rough guide, it is adequate for this assessment provided one bears in mind that a correction is needed for children, in whom the head forms a larger proportion of the body surface and the legs correspondingly less. To assess the body surface of a child's head and neck one should take the age of the child from the number 12, and add the result to the figure for the adult head and neck (9%); the result of the subtraction should be taken away from the combined surface-area figure for both legs (adult 38%). Another measure is the patient's outstretched palm and fingers, which comprise 1% of the body surface.



"Rule of nines" diagram for estimating area of burn.

Blood pressure is a late and very unreliable diagnostic guide to burn shock. A patient can lose 25% of his blood volume, an amount sufficient to cause serious renal damage, without his blood pressure falling. This does not mean, of course, that the blood pressure should not be taken. It should always be taken at intervals when possible, but by the time it begins to fall the patient is well advanced in the stage of latent oligaemia, and may even be suffering from obvious clinical shock.

Diagnosis of the Colloid Requirement

The second question which must be answered is: "How much colloid should be given, and how fast?" It is a tragic admission, but unfortunately true, that rule-of-thumb methods are much too widely used in the resuscitation of burned patients. This is no criticism of the methods themselves. They have a valuable place in the treatment of mass casualties and similar emergencies, but to give individual patients in peace-time average requirements is inexcusable, even if it means that the doctor can leave the treatment of the patient to a nurse while he gets on with other work or goes to bed.

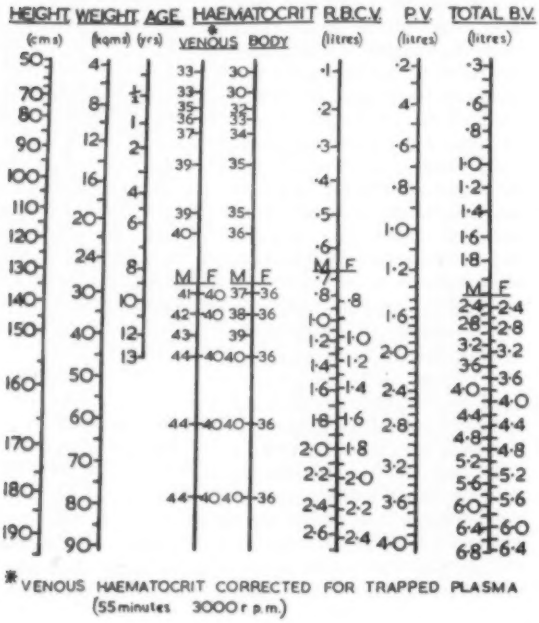
There are at least five good guides to the colloid requirement of the burned patient, and we cannot afford to be without any of them.

1. *Physical Signs.*—If the patient is pale, cold, restless, and with collapsed peripheral veins, these signs indicate oligaemia, and further colloid is required.

2. *The Haematocrit.*—The haematocrit level of the patient before his accident is of course unknown, but there are tables of average values according to age and sex, and initially the patient can be assumed to have an average value unless his first reading on admission is lower than this (see Table). Naturally, one must bear in mind that the patient may have been anaemic before his accident, but in this country one can rule out in this connexion the possibility of polycythaemia. From the initial haematocrit estimation, taken when the infusion is set up a few minutes after admission, the doctor can work out how much plasma has been lost if he assumes that the patient has a normal red-cell volume. This amount of plasma, together with the amount that is going to be lost in the next hour, should then be given in the first hour of infusion, so that by the end of this time the patient's blood volume is returned to normal. If the patient was anaemic before his accident

*Based on a communication read to the Section of Accident Surgery at the Annual Meeting of the British Medical Association, Birmingham, 1958.

Table Showing Average Normal Values. The Venous Haematocrit Values have been Corrected for Trapped Plasma by Subtracting 2% if the Centrifuge Haematocrit is 20–29%, 3% if Between 30 and 49%, and 4% if Between 50 and 69%. The Body Haematocrit Level is the Proportion of the Body Red-cell Volume to the Total Blood Volume: In Practice it may be Calculated by Multiplying the Corrected Venous Haematocrit Value by 0·9



an insufficient amount of colloid will have been given, and perhaps he will still show signs of shock at the end of an hour's resuscitation; in this case the haematocrit level should be brought 5–10 points below normal in the next hour. In practice, too much colloid will never be given in the first hour if the haematocrit is simply brought back to the average normal for age and sex.

3. *Rate of Urine Flow.*—If the burn covers more than 20% of the body surface a urethral catheter is advisable to obtain an hourly figure for urine output. Usually it is not put in place until after the infusion has been set up, so that the bladder is not emptied for perhaps half an hour after admission and the hourly urine output is not known for a further hour after this. This guide is therefore of little value until the second hour. A urine output of 35 to 60 ml. an hour for an adult may be regarded as satisfactory; this is 60–100% of the normal output. Corresponding amounts for children of 3–5 years, who are so commonly burned, are 15 to 25 ml. As mentioned above in connexion with the haematocrit, comparison with average figures can be misleading: the patient may develop some degree of renal insufficiency as a result of prolonged oligaemia, and this may be either oliguric or non-oliguric in type; nevertheless, for most cases the hourly urine flow is most valuable.

4. *A Formula.*—There are many formulae giving the average colloid requirement for patients of known body weight and size of burn. Some are more complicated than others, but all of them are a rough measurement only. A patient's colloid requirement judged by using all the guides together may vary from the formula assessment by as much as 100% or more. The formula I prefer, which has the advantage of being simple, is that a patient will require an amount of colloid equal to his plasma volume for every 15% of the body surface burned, excluding erythema. To use this formula one needs to know the average plasma volume for the patient's height, or height and weight (see Table). This formula gives the colloid requirement of the patient for the first 24 to 36 hours. About half this amount should be given in the first eight hours and the rest during the subsequent 16 to 28 hours of the shock period. This is a formula for colloid replacement only; further fluid must be given to meet the water loss from the kidneys, skin, and lungs, either by mouth or intravenously, if the patient is vomiting.

5. *Estimations of Blood Volume.*—The four guides given above do not always point in the same direction, and when doubt remains about the rate at which colloid should be given, a fifth guide—estimation of patient's blood volume—becomes the decisive factor. There are several ways in which the blood volume can be estimated, but the best at present is probably by a direct estimation of the red-cell volume using radioactive phosphorus or chromium. In a burns unit, facilities to get this estimation done rapidly and to have the answer in one to two hours should always be available.

No one of the guides mentioned is good enough to use alone, but they should all be considered together and the trend of them followed.

Diagnosis of Destruction of Red Cells

Red cells are destroyed in severe burns by loss from the body as haemorrhage, by destruction by heat in the burn, and by subsequent lysis in the circulation by a process which is still ill-understood.

As in the case of plasma loss, there are five useful guides to the amount of red-cell destruction.

1. *Visible Evidence.*—Red cells may be lost from the body in the urine as haematuria or haemoglobinuria. The patient may have a haematemesis, coffee-grounds vomit often being produced even where there is no definite ulcer in the stomach or duodenum. Sometimes there may be a melaena, and, rarely, haemolytic jaundice.

2. *A Count of Fragmented Red Cells.*—In addition to these obvious signs of blood loss there are accessory investigations which are valuable. Fragmented red cells may be seen and counted in a blood film taken on admission to hospital (Topley and Jackson, 1957). About half the cases which have more than 2% of heat-fragmented red cells in the head of the film have moderate red-cell destruction—that is, more than 25% of the red-cell volume destroyed in the first 48 hours.

3. *Signs of Shock with a Normal Haematocrit Level.*—A third sign of red-cell destruction is the persistence of physical signs of shock, such as pallor, restlessness, and a cold nose, forehead, and extremities, after the haematocrit level has been brought back to the average normal figure by colloid infusion. If the patient is still shocked at this stage, either he was anaemic before the accident or red cells were destroyed after the burn.

4. *Falling Haematocrit Level in Absence of Over-infusion with Colloid.*—A fourth guide is a low and steadily falling haematocrit level which is not due to over-infusion with colloid; this may be seen the same hour as the onset of haemoglobinuria.

5. *Estimation of Red-cell Volume.*—This is the same as the fifth guide to the correct colloid requirement—an estimation of the patient's individual red-cell volume.

Because all these guides are rough ones, none should be taken separately, but in conjunction with the others. Even the estimation of the red-cell volume can be deceptive. It is not only subject to the errors of the method, but there is evidence also that stagnation of red cells occurs somewhere in the body during the shock stage in 20–40% burns, and there may be subsequent remobilization of almost 20% of the red-cell volume at the end of this period. Owing to this factor the estimation of the blood volume may have an error of ±20%.

The size of the burn has been purposely left till last. It may be asked whether there is not a simple and useful correlation between the size of deep burning and the degree of red-cell destruction. Unfortunately there is only a rough relationship, and the red-cell destruction in extensive burns is characterized more by variability in the amount and time of red-cell destruction than by correlation with size. Replacement of red cells by a formula may therefore be too little or too much.

In the absence of facilities for measuring the red-cell volume, however, the rough correlation is an available second-best. If a burn is less than 20% of the body surface the red-cell destruction will probably be less than 10% of the red-cell volume. If the burn is 20 to 40% of the body surface, with an average amount of deep burning in it, the red-cell loss is likely to amount to about 20% of the red-cell volume. If the burn is more than 40% of the body surface, the red-cell destruction may vary widely between 20 and 70% of the red-cell volume, sometimes occurring mostly in the first day and sometimes in the second.

It should be emphasized, of course, that keeping the red-cell volume normal except in cases of massive red-cell destruction is of little importance compared with maintaining the blood volume at near normal levels. Knowledge of the red-cell volume and haematocrit level provides a blood-volume figure which is of great value when other guides are conflicting. It is particularly valuable, too, in oliguric renal failure when one wishes to give as little fluid as possible while being sure that enough colloid has been infused to prevent further ischaemic renal damage.

Diagnosis of Renal Insufficiency

Oliguria in burns shock may be physiological or pathological: it may be the result of oligaemia or of renal damage. In some conditions the specific gravity of the urine might be regarded as an index of renal function, even a small amount of concentrated urine suggesting no serious renal damage. In severe burns, however, glycosuria is often present in the first one or two days, and if dextran has been used for colloid replacement this may also be excreted in the urine in sufficient amounts to give a high specific gravity. For these reasons the concentration is more usefully determined by the freezing-point.

A better early test of renal function is the water tolerance test (Cope and Moore, 1947). In the presence of oliguria due to oligaemia a rapid intravenous infusion of a half to one litre of 5% dextrose in water will produce a brisk response in renal output in the next hour. If the renal output is not increased this is evidence of renal damage.

A large hourly urinary output is not a sure indication that all is well. It may be due to over-transfusion, or it may be due to the non-oliguric type of renal failure in which the kidney passes much water but with little in it. The guides of renal function which should be used routinely after the shock stage are estimations of blood urea, which should be carried out on the second, fourth, and sixth days after extensive burning, and daily checks on the urine volume, urea concentration, and osmolarity. With these it should be possible to diagnose renal insufficiency within 24 hours of its onset, and to alter treatment according to whether renal failure is oliguric or non-oliguric in type.

Oliguria is sometimes encountered after the shock stage, between the third and seventh days; although this may be due to renal failure it may also be due to dehydration. It is perhaps not sufficiently appreciated that as much as two litres a day of exudate may be lost from an adult's extensive burns, so that if the correct fluid intake is estimated without this factor the patient may be several litres of water short by the end of the first week. Loss of elasticity of the skin is a good sign of dehydration, and the diagnosis must not be excluded because the veins are full or because there is some residual oedema.

Diagnosis of Electrolyte Imbalance

When oral feeding is started on the second day and renal function is normal, there need be little concern about electrolytes. But if oral feeding has been impossible owing to vomiting, or if there is evidence of inadequate renal function, daily blood chemistry examinations are necessary.

Sodium Deficit.—A low serum sodium level is common between the third and seventh days in burned patients who are progressing favourably. It is not a sign of sodium deficit; in fact, there is a positive sodium balance in the body as a whole due to the colloid (and saline) infusion which has formed the oedema. If normal feeding is not started at the end of the shock stage the serum level may fall to 115–130 mEq/l. In this condition any augmenting factor, such as even slight overhydration with intravenous 5% glucose, may precipitate convulsions or coma.

Sodium Excess.—This is rarely seen with the treatment advised above when dried plasma is reconstituted with 400 ml. of water (sodium concentration 165 mEq/l.). However, hypernatraemia (serum sodium >160 mEq/l.) has been seen in large burns during the stage of absorption of oedema when non-oliguric renal failure is present with water diuresis and sodium retention. Treatment must then steer between dehydration, which is likely to increase the serum sodium level further, and hydration, which may cause pulmonary oedema.

Potassium Deficit.—The burned patient usually maintains a normal daily potassium excretion, and, provided adequate feeding is started on the second or third day, he will not develop a serious deficit. If, however, feeding is impossible, sufficient potassium should be given intravenously to cover the loss in the urine. This may be about 50 mEq a day for an adult and 30 mEq for a child, but it should be measured in the 24-hour collections of urine. It is well known that serum potassium levels are valueless as an index of the potassium balance in the body, because it is held for the most part in the tissues. This tissue reservoir is usually heavily drawn upon before the serum level falls.

Potassium Excess.—This is found in burned patients only when the potassium output is blocked by oliguric renal failure. A rise in serum potassium follows, but again it is a poor index of the balance in the tissues. In this condition every means must be used to prevent potassium intoxication by restricting intake, giving adequate glucose with insulin, and employing at the right time the methods available for potassium withdrawal—for example, ion-exchange resins and the artificial kidney. Even where the serum potassium level is kept within normal limits death may still occur from renal failure.

Diagnosis of Bacterial Colonization and Infection

Bacteriological diagnoses in burned patients are often urgent and vital. Survival may depend on knowing the variety of pathogens which colonize the burn surface, whether invasive infection is present, whether there is a positive blood culture, and if so whether it signifies a transient bacteriaemia or septicaemia. In pulmonary infection the identity of the predominant organism is required and its sensitivity. In addition a decision must be made on the choice of local treatment for each burn.

Bacterial Colonization.—Diagnosis of the flora colonizing the burn should be made frequently so that the patient can be isolated and appropriate treatment given if important pathogens are found. By " important pathogens " one means those harmful to the " take " of skin grafts or resistant to most available antibiotics. Group A β-haemolytic streptococci are the most damaging to graft-take, with *Pseudomonas pyocyanea* and coliform bacilli second ; *Staphylococcus aureus* and Groups C, D, and G β-haemolytic streptococci are less important in this respect. Although in the past some surgeons have belittled the importance of bacterial colonization on the grounds that some degree of it is usually inevitable, this is a quite unrealistic attitude, as much can be done to limit the amount of bacterial growth. Moreover, there is no chance of invasive infection unless the burn is first colonized.

Invasive Infection.—Pain is the principal sign of invasive infection in burns. Redness of the wound edge, excessive discharge, and pyrexia are also significant, but less so. In the exposure treatment of burns the surgeon should not be lulled into a sense of false security by reports of sterile swabs from the dry surface of the eschar ; the under surface may at the same time be bathed in pus containing many organisms.

Positive Blood Cultures.—The frequency with which positive blood cultures are found in burns increases with the thoroughness of the search for them. What do they mean ? If a bacteriaemia occurs after dental extraction, how much more frequent must it be when a patient is lying on an extensive granulating wound. A patient with a positive blood culture is not always clinically ill, and it is possible that the positive result in these cases signifies a bacteriaemia only. At present, however, a septicaemia should be diagnosed and treated with all seriousness when a burned patient has a positive blood culture with a pathogenic organism. A quick bacteriological investigation is called for to diagnose the organism and assess its sensitivity, as the patient's life is at stake.

Pulmonary Infections.—One of the chief difficulties in treating pulmonary infections in burned patients is to find the predominant organism in the lungs so that the condition may be treated with the appropriate antibiotic. This is often an organism which has first colonized the burn. A post-nasal swab usually gives the same predominant organism as that found in the lungs, and we have used this method of diagnosis for several years.

Local Treatment.—The choice between dressings and exposure for local treatment demands an independent assessment for every patient. If practised efficiently both methods are good, and both practised negligently or without experience can be very bad. The surgeon should assess for each burn site in each patient the method which will give the best result in this particular circumstance. Factors to be considered are the time since injury and the condition of the burn. A recent clean burn on a limb can often be better protected from infection by an efficient closed dressing. On the other hand, an infected burn with excessive discharge and contaminated with *Ps. pyocyanea* can often be greatly improved in a few days by exposure and drying. Some parts of the body, such as the limbs and trunk, can be efficiently covered with dressings ; other sites, such as the face, buttocks, and genitalia, are very difficult to dress efficiently and are better left exposed. Further factors are the facilities for doing dressings, the temperature of the environment, and the privacy of the patient's accommodation. There is no reason why both methods should not be employed in the same patient at the same time ; for instance, the face may be treated exposed, and both hands and arms dressed and elevated with the fingers held in the position of optimum function in dressings.

Diagnosis of the Depth of Burning

This is one of the most important early diagnoses that should be made. If the general practitioner can diagnose that the burn is partial thickness skin loss only, he can dress the burn himself, confident that healing will be complete in three weeks without scarring. If the surgeon can diagnose full-thickness skin destruction he can excise and graft the burn on the day of injury. Although experience is valuable we are not without helpful criteria which can be passed on by word and picture.

Perhaps the first lesson the clinician must learn is the deceptiveness of the appearance of burns. A white or charred burn, especially on the face, may turn out to be partial-thickness skin loss and be healed in a fortnight without scarring. On the other hand, a burn may be red, appearing little different from the erythema of a superficial burn, and yet turn out to be full-thickness skin loss. Although the appearance of a burn changes during the next few days and weeks, *no new appearance or physical sign appears during the first week which makes diagnosis easier than it was on the first day.*

There are usually three zones present in a typical fresh burn, and these zones indicate three intensities of burning. The outer one is the zone of hyperaemia, which is red and blanches on pressure, the colour returning with release. This zone remains red, with normal circulation, and by the end of a week is dry and re-epithelized. The middle zone, or zone of stasis, has a circulation for a period after injury, but within a matter of minutes or hours the circulation ceases and the capillaries are left stuffed with red cells. At first this zone is bright red and blanches on pressure, but when the circulation ceases it becomes mottled red and white and no longer blanches. The central zone is white, or even charred, and is the zone of coagulation. One should think of these three zones *in depth* as well as on the skin surface. According to the duration and intensity of burning, they may be shallow or deep although presenting the same surface appearance. The appearance of the burn informs about the upper surface of the skin ; the only part of it we are anxious to know about is its deep surface.

Fortunately the sensitivity of the skin to pin-prick is helpful in determining the viability of the deeper layers of the skin. If, in this test, the patient can feel repeated firm pin-pricks as pressure only, analgesia is present. The interpretation of the test is this: if the

patient can appreciate pin-prick as sharp, the burn is partial-thickness skin loss only, and it will heal without grafting in less than three weeks and leave no scar. The converse is *not* always true: if the burn is analgesic to pin-prick the burn is not necessarily full-thickness skin loss. It is either deep partial- or full-thickness skin loss. Even this knowledge is valuable to the surgeon. The skin in some regions, such as the dorsum of the hand or foot, heals badly after deep partial burning. In such cases excision and replacement with a thick split skin graft may be better.

There are exceptions to the sensitivity test. The face and scalp, and the palms and soles, have epithelial elements penetrating more deeply into the subcutaneous tissue than other parts of the body, and the pin-prick test should never be used in these areas. Similarly, it should not be used where the burn has been produced by chemicals, such as phenol, which have an analgesic action. It goes without saying that this test, like all the others mentioned earlier, should never be used in isolation, but in conjunction with knowledge of the anatomy of the skin and the history of the burn.

Yet another valuable sign in diagnosing the depth of necrosis when excising a deep burn is the red fat in the deeper part of the zone of stasis. This fat is dead. For three or four days after burning the zone of stasis in the skin and fat remains red, but after this time the red cells packing the capillaries lyse, and the avascular fat once more becomes white and difficult to distinguish from the normal fat beneath it.

Summary

The diagnostic problems of burns are discussed in this paper in the order in which they are usually encountered clinically.

The patient requiring resuscitation with colloid infusion may be diagnosed by the proportion of skin surface burned.

The amount and rate of colloid infusion may be assessed from hour to hour by following the changing trend of five clinical guides taken together—the general condition of the patient, the haematocrit level, the urine output, a formula, and measurement of the blood volume.

Whether blood transfusion is required depends on the degree of red-cell destruction. Although this varies greatly from case to case, both in amount and in time, it may also be assessed by five guiding factors—visible blood loss, evidence in a blood film, signs of shock with a normal haematocrit level, a falling haematocrit level without over-infusion, and direct measurement of the red-cell volume.

A routine is suggested for the early diagnosis of renal insufficiency; this needs to be differentiated from the physiological oliguria which accompanies oligaemia in the shock stage, or dehydration in the subsequent week. Oliguric and non-oliguric types of renal failure must also be distinguished if appropriate treatment is to be given.

The two criteria for suspecting electrolyte imbalance and for making daily blood chemistry examinations are renal insufficiency and failure to start oral feeding on the second day. Some suggestions are made for avoiding serious deficit or excess.

The rationale behind frequent bacteriological examination of the burn flora is given, and the early diagnosis of invasive infection and the choice of local treatment for the burn are discussed.

Finally, in connexion with the diagnosis of the depth of burning, the deceptiveness of appearance and the value of sensitivity to pin-prick as a sign of partial-thickness skin loss are emphasized.

Constant reassessment of the changing condition of the patient is an essential feature of successful burns treatment. Sometimes it can be measured, sometimes it must be an informed guess; but always the surgeon must be seeking to forestall the likely complications and to recognize in time their small beginnings.

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PREDNISOLONE TRIMETHYLACETATE IN INTRA-ARTICULAR THERAPY

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Since the introduction of the steroids there has been a renewed interest in intra-articular therapy. The compound most often used has been hydrocortisone, and there is a voluminous literature on its effects. Those authors who have carried out controlled trials (Dixon and Bywaters, 1953; Hollander, 1953; Duff *et al.*, 1955; Duff, 1956; Fearnley *et al.*, 1956) are in agreement that hydrocortisone produces symptomatic benefit in many cases, but several authors have found this to be variable. Thus Robinson *et al.* (1955) obtained worth-while benefit in only half of the joints, although treatment was combined with special orthopaedic and physical therapy measures. Duff (1956) gained worth-while benefit of 7 to 10 days' duration on the average in 50% of cases, while in 31% response was poor, and there was no significant response in 19%. Sairanen (1956) obtained the best results in finger-joints. In the knee-joints the results were poor in 44%. Increased benefit was not obtained by large doses of up to 100 mg. or from repeated injections at short intervals. He concluded that new products with a prolonged effect would doubtless be the solution.

The desirable compound for intra-articular therapy is one with a marked anti-inflammatory action but low solubility. In this way an effective local concentration will be maintained for a prolonged period with little systemic absorption. A number of compounds have been derived from prednisone and prednisolone, the delta-1 derivatives of cortisone and hydrocortisone respectively, which have on systemic administration a greater anti-inflammatory activity than that of the parent substances. As prednisolone is the corresponding compound to hydrocortisone it would appear to be the more suitable for intra-articular therapy. The acetate esters of these compounds are of low solubility. The use of suspensions of crystals of fixed dimensions further delays solution. From a very large number of esters of prednisone and prednisolone investigated,

prednisolone trimethylacetate (Vischer *et al.*, 1955) was shown by Desaulles and Meier (1957), using animal experiments, to be the most suitable for local use.

The Investigation

An investigation of the value of prednisolone trimethylacetate in arthritis was undertaken. Knee-joints were used as they are comparatively easy to enter, and we could be reasonably certain of obtaining a number of specimens of synovial fluid from each knee. Results were assessed according to the relief of pain and the improvement in swelling. A study was also made of the cytological and biochemical changes of the joint fluid.

A total of 290 aspirations were carried out in 57 joints. The number of patients was 35—27 (44 joints) had active rheumatoid arthritis, 6 (9 joints) had osteoarthritis with marked radiological changes and severe symptoms, and 2 (4 joints) had recurrent hydrarthrosis. Of the 35 patients 23 were admitted to the wards for the initial period of treatment, and were subsequently seen at regular intervals as out-patients. The remaining 12 were treated entirely as out-patients. During the period of investigation the simple analgesics which the patients had previously been taking were continued, but no other treatment, in particular steroids or physiotherapy, was given. During their stay in hospital they were ambulant. As most of the patients were under close observation in the ward, and as their treatment was otherwise unchanged, apart from the use of prednisolone trimethylacetate, we feel that our results give a more accurate picture of the effects of the drug.

The knee-joints were entered from the lateral aspect at the level of the upper border of the patella. The skin was prepared with cetrimide and spirit. Dry sterile syringes and needles were used. The operators' hands were scrubbed, and a sterile towel was placed below the knee. A weal was raised with lignocaine ("xylocaine") 2%, using a fine needle, and a small quantity (approximately 0.5 ml.) was infiltrated into the tissues. A 10-ml. syringe and serum needle was then used for aspirating the joint. In a few cases, mainly osteoarthritis, where entry proved difficult, a lumbar puncture needle was used. It was not our practice to drain the joint. Usually a small amount (3–5 ml.), enough to permit routine analysis, was removed. The drug was supplied in 1-ml. ampoules containing 10 mg. of a microcrystalline suspension of prednisolone trimethylacetate. We used 20 mg. (2 ml.) as a standard dose. The interval between injections was initially seven days, until effusion had resolved. Thereafter further injections were gradually spaced out and eventually stopped. The number of injections given per joint varied from 2 to 12, with an average of 5.1. The average period of follow-up since the last injection has been 6.1 months.

We have previously commented on the difficulty of measuring changes in joint size accurately (Currie and Will, 1950). Although joint measurements were made, we found it more suitable to tabulate the results into four grades: marked effusion (+++); moderate effusion (++); slight effusion, where there was patellar tap only (+); and no effusion (0). Pain was assessed by arbitrary groups; severe (+++), moderate (++), mild (+), and absent (0). The initial status of the patients with regard to pain and effusion is shown in Table I.

TABLE I.—*Degree of Effusion and Pain Before Treatment*

Grade	Rheumatoid Arthritis		Osteo-arthritis		Recurrent Hydrarthrosis	
	Swelling	Pain	Swelling	Pain	Swelling	Pain
+++	24	19	6	7	4	2
++	17	24	3	2	—	—
+	3	1	—	—	—	—
0	—	—	—	—	—	2

Results

We had been warned by the manufacturers that there might be some local reaction to the injection, with temporary increase in pain. This occurred in only 2 of the 35 patients and persisted for only a few hours, to be followed by relief. The usual response was relief of pain beginning within six hours of injection, and becoming complete within 48 to 72 hours. Resolution of swelling, although consistent, was less rapid and usually required several injections. In the bilateral effusions the two joints always responded similarly to the drug. It is of value to discuss the results under the disease classifications.

Rheumatoid Arthritis

The most rapid relief of pain and swelling was obtained in this group, whose general features are summarized in Table II. Assessment at the end of the follow-up period shows the results to have been good in 23 (85.2%), fair in 2 (7.4%), in that regular maintenance injections have been required, and poor in two (7.4%).

TABLE II.—*Details of 27 Patients With Rheumatoid Arthritis*

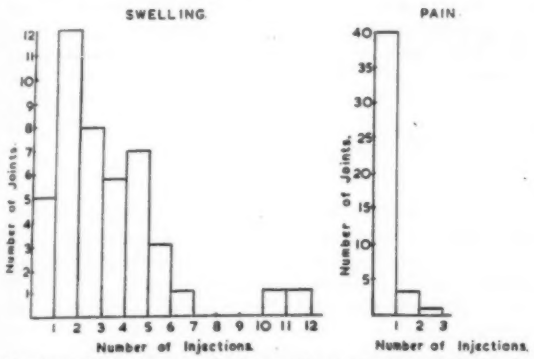
Case No.	Sex and Age	Duration in Years	E.S.R. mm./1 hr.	Nodules	Joints Involved
1	F 56	6	44	—	Wrists, knees, fingers
2	F 47	8	39	—	Knuckles, fingers, elbows, knees, ankles, feet
3	F 55	12	66	—	Wrists, fingers, elbows, knees, ankles
4	F 45	7	22	—	Fingers, wrists, knees, ankles
5	F 66	8	16	—	Fingers, wrists, knees
6	F 36	8	16	—	Fingers, wrists, elbows, knees
7	F 58	3	61	—	" " " "
8	F 40	5	28	—	Fingers, wrists, knees, ankle
9	F 55	12	20	—	Fingers, wrists, knee, ankle
10	F 58	16	47	+	Fingers, wrists, elbows, knees, ankles, feet
11	F 53	6	76	+	Fingers, wrists, shoulders, knees
12	F 50	6	34	—	Fingers, wrists, shoulders, knees, ankles
13	F 45	7	50	—	Fingers, wrists, shoulder, knees, ankles
14	F 58	3	29	—	Fingers, wrists, elbows, knees, ankles
15	F 58	20	38	+	Fingers, wrists, elbows, shoulders, knees
16	F 56	20	58	—	Fingers, wrists, knee, ankles
17	M 43	6	22	—	Knees
18	M 56	5/12	12	—	Wrists, elbows, knee, ankles, feet
19	M 49	4	65	—	Fingers, wrists, elbows, knees
20	M 63	17	20	+	Fingers, wrists, elbows, shoulders, knees
21	M 61	6/12	54	+	Fingers, wrists, knees
22	M 65	4/12	29	—	Fingers, knees
23	M 38	1	30	+	Fingers, wrists, elbows, knees
24	M 60	6	58	—	Fingers, elbows, knees, ankles
25	F 55	22	50	—	Fingers, wrists, knees
26	M 49	8/12	81	—	Fingers, wrist, elbows, knees
27	M 56	3	74	+	Fingers, wrists, elbows, knee, ankles

The following routine investigations were negative in all 27 cases: the blood Wassermann, the gonococcal flocculation test, and the *Brucella abortus* agglutination. The blood uric acid was normal in all patients. The Rose-Waaler test was not carried out routinely.

In one of the poor results—that in a patient with long-standing rheumatoid disease and bilateral effusions—we were unable to space out injections beyond 10-day intervals without recurrence of swelling. Nevertheless

the patient, an ironmongery manager aged 38, who had previously been bedridden, has been able to carry on his business during the past eight months.

The Chart records the number of injections required to produce complete relief of pain and resolution of swelling in these patients.



Number of injections required to produce complete relief of pain and resolution of swelling in 44 rheumatoid joints.

Osteoarthritis

The number of cases in this and the succeeding group are too small to permit detailed analysis. Of the six cases a good result was obtained in two (Cases A and B); a fair result in two (Cases C and D), in that regular maintenance injections have been required; and a poor result in two (Cases E and F).

Case A.—An obese woman aged 64 years had had pain and swelling of both knees for five years. There was moderate effusion in both knees and *x*-ray examination showed marked bilateral osteoarthritic lipping. The E.S.R. was 6 mm. in one hour. After treatment the effusions absorbed and she obtained lasting relief of pain.

Case B.—A night sister aged 50 had a five-years history of pain and swelling of both knees. She was obese, and there were moderate effusions in both joints with marked crepitations on movement. The E.S.R. was 6 mm. in one hour. X-ray examination showed marked osteoarthritic changes in both knees and less severe changes in the right hip and lumbar spine. Since treatment she has been able to resume her duties and to enjoy swimming again.

Case C.—Since an injury to her right knee nine years ago this 63-year-old woman had severe pain in the joint, with swelling and instability. Examination disclosed a large effusion and marked crepitus on movement. The E.S.R. was 6 mm. in one hour. *X*-ray examination showed gross osteoarthritic lipping and loss of joint space. After treatment the effusion cleared, but she needed injections at 10-day intervals to keep her free of pain.

Case D.—A 47-year-old woman had a history of pain and swelling of the right knee for 11 years. There was a moderate effusion into the joint. The E.S.R. was 12 mm. in one hour. *X*-ray examination showed an old healed fracture in the lower half of the right femur with deformity, and there was gross osteoarthritis of the right knee-joint. After treatment there was relief of pain and increased joint movement, but unless injected at fortnightly intervals she tended to relapse. She is, however, able to continue working as a printer's assistant.

Case E.—An obese woman aged 56 complained of pain and swelling of both knees of seven years' duration. The E.S.R. was 15 mm. in one hour. There was thickening of the joints, with crepitations on movement. *X*-ray examination showed marked osteoarthritic changes in both knees with considerable diminution of joint space. Treatment produced no notable change.

Case F.—An obese woman of 52 had had osteoarthritis of the left knee for seven years. On examination there was a large effusion with crepitus on movement and marked muscle-wasting. The E.S.R. was 8 mm. in one hour. *X*-ray examination showed osteoarthritic lipping and diminution of joint space. The effusion cleared after a course of injections, but she did not obtain significant symptomatic benefit.

Recurrent Hydrarthrosis

In both of the following cases the results of treatment were good.

Case I.—A bookbinder aged 32 had had painless swelling of both knees for three years. Investigations, including synovial biopsy, serological examination, and repeated culture of the joint fluid, had shown no specific disease. The swelling resolved after four injections in one knee and eight in the other, and there has been no recurrence during the six-months period of follow-up.

Case II.—A housewife aged 36 had had persistent swelling of both knees for one year. The swelling completely resolved in one knee after three injections and in the other after four injections. There has been no recurrence during the nine-months period of follow-up.

Control Group

Ten patients with bilateral effusions of comparable severity were selected. One knee was used initially as a control. A similar procedure was carried out in both knees, one receiving prednisolone trimethylacetate and the other an equal volume of lignocaine, the patient and one of us being unaware which side was chosen. The control knees received two injections of lignocaine at weekly intervals with the exception of three cases where the marked contrast in pain between the knees after the first injection made it unjustifiable to continue the experiment. When at the end of the control period the active drug was given to the joints having lignocaine, resolution of pain and swelling occurred in all. These results are summarized in Table III.

TABLE III.—*Response of Pain and Swelling to Injection in Control and Treated Groups at End of Control Period*

Degree of Improvement	Pain		Swelling	
	Treated*	Control	Treated	Control
Nil	—	7	—	9
Slight	—	1	3	1
Moderate	4	1	7	—
Marked	5	1	—	—

* One case was painless throughout.

Discussion

The variable results obtained with hydrocortisone acetate may be due to the rapidity with which the compound is absorbed into the circulation. Wilson *et al.* (1955) showed that after an injection of hydrocortisone acetate 86% of the drug had disappeared from the joint at the end of one hour, and 97% at the end of three hours. Thirty minutes after injection, appreciable amounts of what was probably hydrocortisone were found in the uninjected contralateral knee. The findings of Oka (1956) are in general agreement. The plasma 17-hydroxycorticosteroid levels after intra-articular injection of hydrocortisone were found to be so high that systemic hormonal effects were to be expected if large and frequent doses were used. Oral or intra-articular hydrocortisone acetate gave peak blood levels three hours after administration.

Attempts have been made to find a longer-acting steroid compound. Hollander *et al.* (1954) undertook

clinical trials of a number of compounds, including 9 - alpha - chlorohydrocortisone, allo - dihydrohydro - cortisone, and two higher esters—hydrocortisone caprylate and hydrocortisone benzoate. While benefit was obtained in a few cases by one or the other, it was noted that the 9-alpha-chlorohydrocortisone compound could cause fluid retention. The hydrocortisone benzoate preparation gave rise to synovial irritation. None of the compounds gave such consistent improvement as hydrocortisone tertiary butyl-acetate. Duff *et al.* (1955) found hydrocortisone tertiary butyl-acetate more effective than hydrocortisone acetate in 50% of cases. Rothermich and Philips (1957) considered hydrocortisone tertiary butyl-acetate the more effective of the two. In a further paper, Hollander *et al.* (1955) found the tertiary butyl-acetate to give a longer and more complete response in 60% of cases than was obtained with hydrocortisone acetate. Nevertheless in 35% no advantage was noted and in 5% hydrocortisone acetate gave a better result. Freyberg's (1954) findings were less encouraging, since only 39% of his patients responded for a significantly longer period. Zickner *et al.* (1956), however, found that there was no significant difference between hydrocortisone and hydrocortisone tertiary butyl-acetate in degree or duration of improvement.

There are few reports of prednisolone trimethyl-acetate in the literature, and none containing controls. Thompson (1957) reported no significant difference between prednisolone acetate, prednisolone trimethyl-acetate, and hydrocortisone acetate in the treatment of large or medium-sized rheumatoid joints. Glyn and Newton (1958) comment that limited experience has not shown prednisolone trimethylacetate to possess any advantage over hydrocortisone acetate. They were, however, referring to the treatment of soft-tissue lesions.

In chronic disease it is often difficult to evaluate a new therapeutic substance because of the psychological response of the patient to a different form of therapy. In discussing their results of intra-articular injections—to the patient a dramatic form of treatment—few authors appear to have taken this into consideration. Fearnley *et al.* (1956), in a controlled cross-over trial using hydrocortisone acetate or 2% procaine fortnightly for four injections, showed that the only significant difference was that found between the results of the first treatment and that of the second, regardless of which drug was used. Leveaux and Quin (1956) in osteoarthritis of the hip compared procaine with hydrocortisone and procaine in two comparable groups. The results of the first injection in each group were remarkably similar. The results of the second showed the superiority of hydrocortisone. This difference could not be explained on an organic basis. The authors emphasized the influence of psychological factors on the response to first injections.

The results of our control experiment differ from the above in that the active compound was shown to be superior from the start, but we assessed the control and active compounds simultaneously in each patient. This may partly explain the difference. It is also possible that we were dealing with a more potent drug.

It seems likely that the action of prednisolone trimethylacetate is a local one. There was no evidence of general systemic effect on our patients. In particular, the sedimentation rates showed no significant change. There was no improvement in joints other than those injected, and this is well demonstrated by the control group. During treatment there was evidence of fresh activity in other joints in eight patients, whereas improvement in the knees continued.

Our experience over a period of 14 months in the treatment and follow-up study of the patients reported has shown that prednisolone trimethylacetate is an effective agent for intra-articular therapy. In addition, the superiority of the cytological and biochemical changes in the joint fluid produced by the drug (Murdoch and Will, 1959), when compared with those published for hydrocortisone, confirms our view, and merits further study.

Summary

A trial of prednisolone trimethylacetate, a new compound for intra-articular therapy, is described.

57 joints were treated in 35 patients. Of those patients, 27 (44 joints) had active rheumatoid arthritis, 6 (9 joints) had osteoarthritis, and 2 (4 joints) had recurrent hydrarthrosis.

In the rheumatoid arthritis group results were good in 23 (85.2%), fair in 2 (7.4%), and poor in 2 (7.4%). Of the six cases of osteoarthritis a good result was obtained in two, a fair result in two, and a poor result in two. In both cases of hydrarthrosis the results of treatment were good. In 10 patients with bilateral effusions, one knee was used initially as a control, being given an equal quantity of lignocaine.

The results obtained over a period of 14 months show that prednisolone trimethylacetate is an effective agent for intra-articular therapy. It would appear to compare favourably with the reported figures for hydrocortisone. The significance of these findings is discussed.

We thank Dr. J. W. Macfarlane for his continued interest and encouragement, and Dr. J. P. Currie who kindly referred patients to us. Dr. C. D. Falconer, medical director, Ciba Laboratories, made a generous supply of prednisolone trimethylacetate ("ultracortenol") available. Finally this trial would not have been possible without the willing co-operation of the sisters in wards 10 and 11, Glasgow Royal Infirmary, and ward B4, Eastern District Hospital.

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SYNOVIAL FLUID CHANGES IN INTRA-ARTICULAR THERAPY

EFFECT OF PREDNISOLONE TRIMETHYLACETATE

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There are many reports on the clinical effects of hydrocortisone and related compounds in intra-articular therapy, but few authors seem to have made a detailed study of the changes in synovial fluid. While undertaking a clinical trial of prednisolone trimethylacetate (Murdoch and Will, 1959) we decided to make observations on the cytological and biochemical characters of the synovial fluid in an attempt to detect changes which might occur, and to establish their possible relationship to clinical improvement.

Method

Knee-joints were investigated. In the course of the trial injections were given at weekly intervals, and were then gradually spaced out and eventually stopped as improvement occurred. Before each injection a small amount (usually 3 to 5 ml.) of joint fluid was removed for analysis. The mucin content was estimated by the acetic acid method (Ropes and Bauer, 1953). Viscosity was assessed clinically into one of three grades: slight, moderate, or marked. A portion of synovial fluid was put into a sequestrene bottle to prevent clotting, and the remainder into a plain glass tube. A total white-cell count was done on the sequestrene specimen within two hours of removal. A thin film was made, fixed with heat, stained with Leishman, and a differential cell count carried out. The total protein was estimated by a modification of the biuret method (Gornall *et al.*, 1949). Electrophoresis was carried out, in a free hanging horizontal tank, using Whatman No. 3 paper and a barbitone buffer of *p*H 8.6 (Jencks *et al.*, 1955). After staining and drying the strips, ammonia vapour was used to intensify the colour, and they were scanned in a recording photo-densitometer. The total surface area of the densitometer tracing and the individual areas of the protein fractions were estimated with a planimeter, and it was thus possible to obtain the percentage distribution of the various fractions. From the total protein figure the absolute values could be obtained.

Results

Fifty-seven joints were aspirated. In 17 joints there were too few samples owing to rapid resolution of effusion or contamination with blood. In the remaining 40 a sufficient number of suitable serial specimens were available for detailed study of viscosity, mucin content, total and differential cell counts, protein content, and electrophoretic pattern during therapy. These comprised 30 rheumatoid joints, 6 osteoarthritic joints, and 4 joints with hydrarthrosis. The findings are discussed separately under the disease headings.

Rheumatoid Arthritis

In these effusions the fluid was usually watery, pale yellow, and turbid. Fibrin flakes were present, and clotting occurred on standing. The cell content was high and polymorphonuclear cells predominated.

Marked changes occurred in the cell count during treatment with prednisolone trimethylacetate. The initial average cell count was 6,936 per c.mm., with a wide range (1,000 to 36,000 per c.mm.). At the end of treatment there was a fall in every case, the average cell count being 1,163 per c.mm. These results are summarized in Fig. 1.

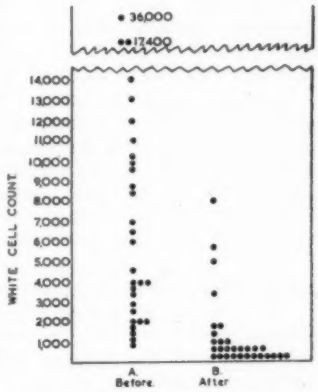

FIG. 1.—White-cell count before and after treatment with prednisolone trimethylacetate in 30 rheumatoid joints.

In performing the differential count the four mononuclear types described by Ropes and Bauer (1953) were identified. For convenience in assessing the results, however, the cells were placed into three groups: polymorphs, lymphocytes, and monocytes. The initial differential count showed a polymorphonuclear predominance in all but one joint, the average figure being 74.4%. Most of the fall during treatment was due to a sharp diminution in polymorphs, with the appearance of a relative lymphocytosis. Examination of the absolute figures, however, showed a real drop in all three types—namely, polymorphs 84.7%, lymphocytes 42.6%, and monocytes 67.1%.

The initial average protein was 4.4 g. per 100 ml. (range 3.35 to 5.6 g. per 100 ml.). 28 joints showed a fall after treatment with prednisolone trimethylacetate, 1 was unchanged, and 1 showed a rise. The final figure was 3.4 g. per 100 ml. (range 2.3 to 4.9 g. per 100 ml.) representing an average drop of 1.0 g. per 100 ml. These results are summarized in Table I.

TABLE I.—*Initial and Final Proteins (g. per 100 ml.) in 30 Rheumatoid Joints*

	2–	2·5–	3–	3·5–	4–	4·5–	5–	5·5–6
Initial	—	—	3	5	9	7	5	1
Terminal	4	9	5	6	3	3	—	—

TABLE II.—*Initial and Final Albumin Percentage in 30 Rheumatoid Joints*

	30%–	40%–	50%–	60%–	70+%	Total
Initial	18	5	6	1	—	30
Final	6	8	11	4	1	30

In studying the electrophoretic changes it is of value initially to add the globulin fractions together so that the main trends in the albumin:globulin ratio can be observed. The average initial albumin proportion was 40% (range 30.5 to 67.6%). During treatment 33 of the joints showed a rise in albumin content, while 8 showed

a drop, which was usually small. The final average albumin percentage was 50.8% (range 30.7 to 74.5%) (Table II). Detailed analysis of the globulin fractions showed that in three joints the diminution was due largely to a fall in α_2 content, in three joints to a fall in γ-globulin, and in a further three there was a fall of both α_2- and γ-globulin. In the remainder the diminution was spread through all globulin fractions. A fast-moving component ahead of the albumin band was found in one case on one occasion only.

There was usually a rise in viscosity following treatment. Thus viscosity increased in 11 joints by two grades, and in 15 by one grade. There was no change in three joints, and in one there was a fall by one grade.

Interpretation of the mucin test by the acetic acid method proved unsatisfactory, and it was often difficult to classify the clot in the grades suggested by Ropes and Bauer (1953). In contradistinction to most authors who show a rise in mucin content after treatment, we found a fall of two grades in 10 joints and of one grade in 17 joints. In three joints there was no change.

A typical response to a course of injections with prednisolone trimethylacetate was progressive reduction in the volume of the effusion, accompanied by an increase in viscosity. The marked decrease in the total cell count and the changes in the differential count usually occurred after the first two injections. The changes in total protein and the albumin content were more gradual, however. By the end of treatment only a few drops of clear viscid fluid could be obtained. Fig. 2 (a) is an example.

Globulin Fraction and Duration of Disease in Rheumatoid Arthritis.—Several authors have reported a direct relationship between the γ-globulin content and duration of disease (Ropes *et al.*, 1949; Olhagen, 1950; Ropes and Bauer, 1953). The initial electrophoretic patterns in 40 rheumatoid joints are grouped according to duration in Table III. There would appear to be no direct increase of γ-globulin with duration.

TABLE III.—*Electrophoretic Analysis of Synovial Fluid Protein in 40 Rheumatoid Joints*

No.	Total Protein g./100 ml.	Albumin %	α_1-Globulin %	α_2-Globulin %	β-Globulin %	γ-Globulin %	Duration
1	3·9	57·1	4·2	10·55	10·55	17·6	4 months
2	3·8	32·9	6·8	15·6	20·6	24·1	4 ,,
3	4·3	38·05	5·8	14·4	15·15	26·6	6 ,,
4	4·7	34·6	6·25	15·15	15·15	28·85	6 ,,
5	4·9	50·9	6·3	5·0	15·1	22·7	8 ,,
6	5·0	40·6	8·0	13·3	9·1	29·0	8 ,,
7	4·6	39·8	5·0	9·4	12·2	33·6	20 ,,
8	5·25	46·2	4·5	8·6	13·7	27·0	20 ,,
9	5·6	51·0	7·3	5·3	6·4	30·0	3 years
10	5·3	38·2	7·9	14·0	21·9	18·0	4 ,,
11	4·4	37·0	6·8	13·7	17·4	25·1	4 ,,
12	3·7	32·2	11·1	9·5	12·7	34·5	6 ,,
13	4·1	33·5	9·6	8·7	14·8	33·5	6 ,,
14	5·45	35·8	3·2	8·9	17·4	34·7	6 ,,
15	4·9	32·8	5·6	11·4	6·3	43·9	6 ,,
16	4·2	47·0	6·8	6·0	11·7	28·5	6 ,,
17	4·2	31·3	7·1	10·9	21·6	29·1	6 ,,
18	4·7	53·1	5·4	3·4	6·7	31·4	6 ,,
19	3·7	49·83	10·0	16·0	10·53	13·64	6 ,,
20	3·9	58·0	4·6	1·9	11·3	24·2	7 ,,
21	4·7	51·9	5·2	8·6	14·5	19·8	7 ,,
22	3·35	52·9	3·1	4·5	16·5	23·0	7 ,,
23	3·9	50·1	3·1	12·7	13·7	20·4	7 ,,
24	5·4	40·2	5·7	11·2	20·8	22·1	7 ,,
25	4·3	35·0	2·2	16·5	30·6	15·7	8 ,,
26	3·36	41·3	5·3	2·5	19·6	31·3	8 ,,
27	4·3	35·5	4·5	9·9	15·6	34·5	8 ,,
28	4·0	49·7	3·6	12·1	13·44	21·16	8 ,,
29	5·1	49·5	2·2	6·4	14·8	27·1	8 ,,
30	3·4	36·6	9·05	17·1	13·0	24·25	9 ,,
31	3·15	47·2	6·85	10·15	12·1	23·7	9 ,,
32	5·1	34·9	2·4	13·9	13·1	29·4	10 ,,
33	4·9	38·6	8·8	17·7	8·1	26·8	10 ,,
34	4·1	30·5	3·0	8·6	13·4	44·5	12 ,,
35	4·7	39·3	12·7	6·35	11·15	30·5	12 ,,
36	4·1	37·5	5·8	4·2	12·0	40·0	17 ,,
37	3·0	51·0	11·4	7·1	10·0	20·5	20 ,,
38	4·1	67·6	4·66	6·11	6·11	15·42	20 ,,
39	4·8	37·6	9·1	11·8	12·9	28·6	23 ,,
40	4·5	31·9	5·45	6·06	12·39	44·2	23 ,,

Osteoarthritis

The joints in this and the succeeding group are too small in number for detailed analysis. Six were available for serial study. The fluid obtained was usually clear, pale yellow in colour, moderately viscous, and did not clot on standing. The initial average cell count was 2,316 per c.mm. (range 200 to 4,000 per c.mm.). Before treatment there was a polymorphonuclear predominance, with the appearance of a relative lymphocytosis after therapy. The absolute figures indicated a fall in all three cell types.

The protein content was lower than in rheumatoid arthritis, the average being 3.3 g. per 100 ml. The final figures show a fall to 2.3 g. per 100 ml. The initial albumin content was 48.9% which is higher than in rheumatoid arthritis. A rise to 59.8% occurred after treatment. There was a slight rise in viscosity.

Hydrarthrosis

There were two patients with bilateral effusions. The synovial fluid of the two cases showed marked differences. In one, the knees showed a high cell count of 14,000 and 40,000 per c.mm. respectively, with a lymphocytosis of 80%. The total protein was high: 4.5 and 4.2 g. per 100 ml., with an albumin of 65.2% and 68.9%. In response to treatment there was an increase of viscosity. The cell counts fell to 400 and 800 respectively, but the differential was unchanged. Total protein dropped to 3.3 and 3.35 g. per 100 ml., with a diminution of approximately 10% in the albumin percentages of both.

In the other case the findings and response to treatment resembled the rheumatoid group.

Control Group

Ten patients with bilateral effusions of comparable severity were studied. Injections were given at weekly intervals, the control knee receiving an equal volume of lignocaine on two occasions in seven of the cases, and once in the remaining three, instead of the active agent. Thereafter both knees were given prednisolone trimethylacetate. In contradistinction to the treated knees there was no change in mucin and viscosity content in the controls. The cell counts rose in six, and were unchanged in the remainder. In four the total protein rose, remaining unchanged in the other six. An analysis of the electrophoretic strips of the group showed no significant change. A typical example is shown in Fig. 2.

Correlation Between Clinical Effects and Laboratory Changes.—With the exception of one patient, whose joint fluid showed little change, although relief of pain and swelling occurred, clinical improvement was directly associated with the cell and protein changes described above.

Discussion

Most authors who have studied the characters of the synovial fluid are in agreement that there is a drop in the total white-cell count after treatment with hydrocortisone acetate (Duff *et al.*, 1951; Kersley and Desmarais, 1953; Duff *et al.*, 1955; Austen and Calkins, 1955). They claim that the mononuclear cells are unaltered, the fall being due to a diminution of polymorphonuclear cells. Robinson *et al.* (1955),

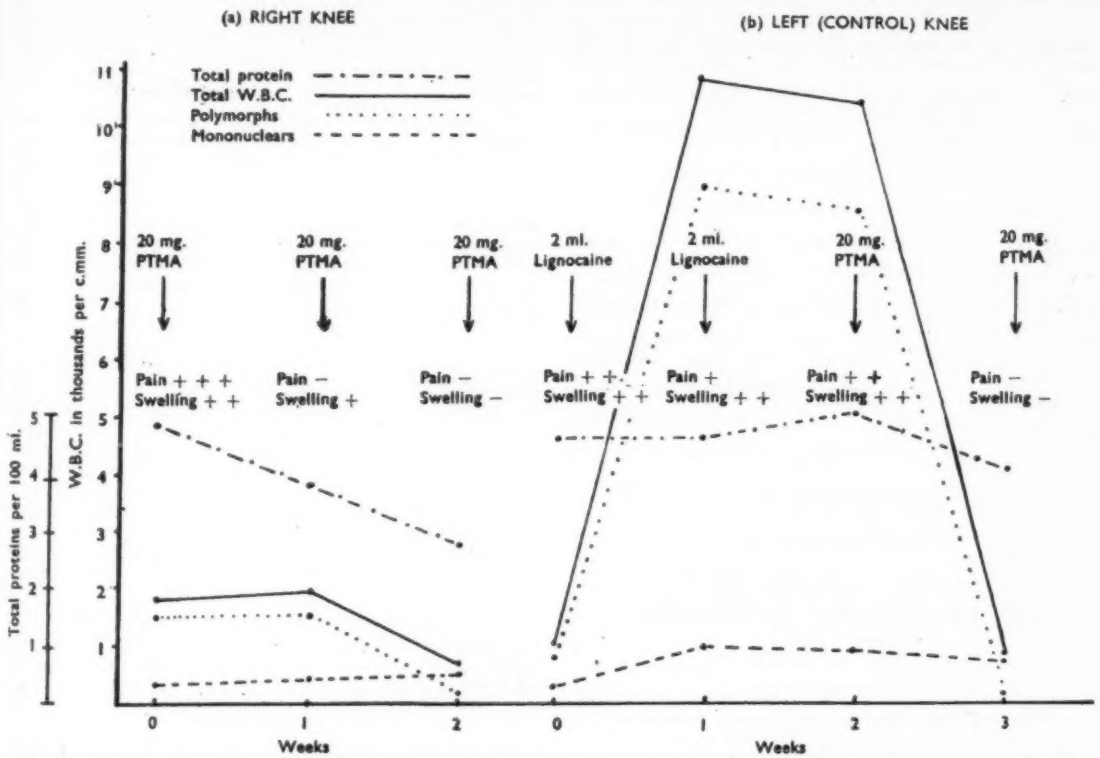

FIG. 2.—Changes in total protein, white-cell count, polymorph and mononuclear counts in (*a*) the right knee treated with prednisolone trimethylacetate, and (*b*) the left (control) knee given initially an equal volume of lignocaine ("xylocaine").

however, found that these changes were not consistently obtained, and lasted for only a few days. Our figures show a persistent fall in the total white-cell count after treatment with prednisolone trimethylacetate, but analysis of the absolute counts shows a real diminution in all cell types.

Those who comment on the synovial fluid protein find little or no change in the total protein concentration after treatment with hydrocortisone or hydrocortisone acetate (Dixon and Bywaters, 1953; Jessar *et al.*, 1953; Sunblad *et al.*, 1954). Our findings are in marked contrast. Whereas the total protein rose in two joints and remained unchanged in one, there was a consistent fall in the remaining 37 joints of the series. Ziff *et al.* (1953) found no change in either total protein or albumin:globulin ratio. Yielding *et al.* (1956) found that the true albumin could not be estimated in joint fluids by salting-out methods. The electrophoretic technique permits effective separation of the albumin, and, in addition, of the various globulin fractions. We have not seen reports of previous serial studies using this method. Jessar *et al.* (1953), in examining four pairs of joint fluid by the Tiselius method, found no change in the electrophoretic pattern after one injection of hydrocortisone acetate. They found in each case a fast-moving component in front of the albumin band having the same mobility as hyaluronic acid. It is of interest that this band was found in only one of our tracings. We found the albumin content to be increased in 28 of the 40 joints studied.

In keeping with the findings of other authors (Dixon and Bywaters, 1953; Kersley and Desmarais, 1953; Ziff *et al.*, 1953; Duff *et al.*, 1955; Robinson *et al.*, 1955; Yielding *et al.*, 1956) there was an increase in viscosity with treatment in the majority of cases.

On examination of the mucin clot, though the method used was unsatisfactory, we appeared to find a decrease in clot density in response to treatment. However, we found significant protein changes during therapy, and it may be that changes in the mucin clot were partly related to these. We have this aspect under investigation.

Prednisolone trimethylacetate produced greater change in the cell content and pattern of the synovial fluid than has been reported for other steroids. In addition, it is the only compound so far noted to produce significant changes in total synovial protein and electrophoretic pattern. These findings suggest that it has a local action superior to the other steroid compounds used.

Summary

A detailed analysis is made of the serial changes in total and differential cell counts, total protein and electrophoretic pattern, viscosity, and mucin content of the synovial fluid of 40 joints (30 rheumatoid arthritis, 6 osteoarthritis, and 4 hydrarthrosis) treated with prednisolone trimethylacetate, a new compound for intra-articular injection.

The findings suggest a local action superior to that of the other steroid compounds used.

We thank Dr. J. W. Macfarlane for his continued interest and encouragement. We are indebted to Dr. J. C. Eaton, biochemist, Glasgow Royal Infirmary, for laboratory space and, with Dr. W. S. T. Thomson, for helpful criticism of the text

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RAPID DESTRUCTION OF APPARENTLY COMPATIBLE RED CELLS

BY

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As serological tests have improved, it has become progressively easier to avoid the transfusion of incompatible blood. When, owing to weak reactions of the blood-group antibody *in vitro*, incompatibility of a sample of red cells is overlooked, transfusion of the cells is usually followed only by a mild haemolytic reaction.

The case reported here is remarkable in that transfusions of red cells which seemed to be perfectly compatible, judged by tests *in vitro*, were repeatedly followed by severe reactions, with haemoglobinuria.

Case Report

A married woman aged 46 was found in 1955 to have reticulum-cell sarcoma. In 1956 she received deep *x*-ray therapy. During the course of treatment her haemoglobin concentration dropped from 84% to 44%. She was given several blood transfusions, but the notes state that these were "not tolerated." According to the patient the first transfusion took place in February, 1956; she received 2 pints (1 litre) and developed a slight fever, but no other symptoms. The next blood transfusion was given three or four weeks later, and was followed by shivering and high temperature; the next day she was jaundiced.

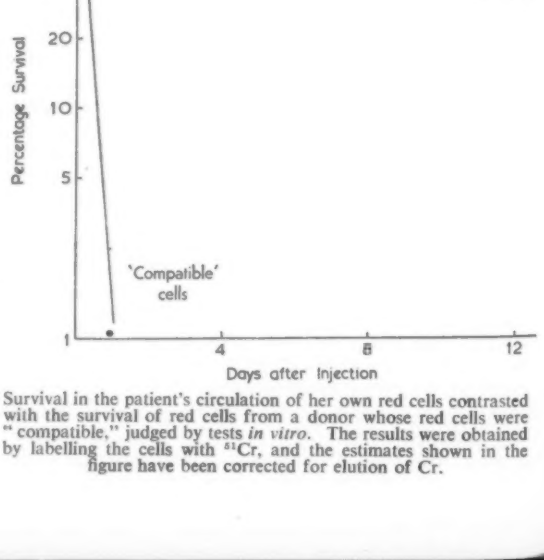
Later in 1956 she was found to have enlarged glands in both groins. Further deep *x*-ray therapy was given. In May, 1957, she received another course of *x*-ray therapy, and a transfusion of 2 pints (1 litre) of blood. The transfusion produced only a transient increase in haemoglobin concentration. In June she was severely anaemic; the results of a blood examination were as follows: haemoglobin, 4.9 g./100 ml.; red cell count, 1,400,000/c.mm.; P.C.V., 15%; reticulocytes, 10%; W.B.C., 1,700/c.mm. (lymphocytes 17%, neutrophils 70%, monocytes 11%, metamyelocytes 2%); 4 nucleated red cells/100 W.B.C.; platelets 51,000/c.mm. The patient had petechial haemorrhages and was bleeding from the gums.

A transfusion with blood which was compatible by the indirect Coombs test and the albumin technique was given, but had to be abandoned after approximately 350 ml. had been transfused because of fever and haemoglobinuria. Treatment with prednisone, 5 mg. four times a day, was then begun. Five days later (June 7), a transfusion of red cells, labelled with ^{51}Cr and washed three times in saline, was given. After the patient had received about half of this over the course of several hours, she felt ill and the transfusion had to be stopped. The urine passed shortly after the end of this transfusion contained haemoglobin; a blood sample showed that most of the injected cells had already been eliminated. The patient's clinical condition improved slightly, but she still suffered from petechial haemorrhages, and her haemoglobin concentration was only 4.5 g./100 ml., with a white cell count of 3,100/c.mm. and a platelet count of 18,000/c.mm. On June 14 the prednisone was increased to 25 mg. four times a day. On July 5 the haemoglobin concentration was 4.8 g./100 ml., and the patient now improved rapidly. By July 25 the haemoglobin concentration had risen to 9.3 g./100 ml., with a platelet count of 187,000/c.mm. The patient was discharged from hospital on a reduced dosage of prednisone (15 mg. three times a day).

When seen in the out-patient department in September her haemoglobin concentration had risen to 12.2 g./100 ml. and her white cell count to 7,800/c.mm. She died suddenly at home in December, 1957.

Red Cell Survival Tests

As mentioned above, a test with ^{51}Cr-labelled red cells was made on June 7, and this showed clearly that the haemolytic reactions were due to destruction of the donor's red cells rather than those of the recipient. On June 13 an attempt was made to measure more precisely the mode of elimination of the injected red cells. Accordingly, a sample of blood was taken from a compatible donor, and 1 ml. of cells was labelled with radioactive chromium and injected. As a control, a sample of the patient's own red cells was labelled with ^{32}P and injected. From the ^{32}P counts in the patient's blood after the transfusion the number of ^{51}Cr



Survival in the patient's circulation of her own red cells contrasted with the survival of red cells from a donor whose red cells were "compatible," judged by tests *in vitro*. The results were obtained by labelling the cells with ^{51}Cr, and the estimates shown in the figure have been corrected for elution of Cr.

counts expected, if 100% of the injected ^{51}Cr-labelled red cells survived, could be predicted. A sample taken eight minutes after injection contained 99% of the expected number of ^{51}Cr-labelled cells; a sample taken 33 minutes after injection contained only 91%, while a sample taken at three hours contained 55%. A sample taken 22 hours after injection contained only 1% of cells (see Chart). The amount of radioactivity in the plasma was measured in all samples, and the largest amount (representing 6.7% of the total ^{51}Cr injected) was found in the three-hour sample.

On June 24 a sample of the patient's own cells was labelled with ^{51}Cr and reinjected to estimate the average life-span of the patient's own cells in her own circulation. The ^{51}Cr-labelled cells were removed relatively slowly, and the average life-span was estimated to be 11 days (see Chart).

Serological Findings

The patient's full blood groups were determined by Dr. D. Parkin, of the Blood Groups Research Unit of the Lister Institute, as follows: O, CcDE, N, S−, P+, Lu(a−b+), K−, k+, Le(a+b−), Fy(a+), Jk(a+b−), Vel+, Yt(a+).

The donor, whose red cells were labelled with ^{51}Cr, had the following blood groups: O, ccddEe, M, S−, P+, Lu(a−), K−, Le(a+b−), Fy(a+). Cells of this donor were tested with the patient's serum before they were injected, and were tested again on two subsequent occasions. No reaction of any kind could be demonstrated using the following tests: agglutination in saline; agglutination in albumin; agglutination of enzyme-treated cells; indirect antiglobulin (Coombs) test against untreated cells; and indirect antiglobulin test against enzyme-treated cells. In case the serum was anticomplementary, the indirect antiglobulin test was carried out in two stages, the cells being first incubated with the patient's serum, then washed and resuspended in fresh serum from a normal donor before being finally washed and tested with the antiglobulin serum.

Haemolysis could not be demonstrated with any of these tests, either when human serum or when rabbit serum was used as a source of complement. (For the possible advantages of using rabbit serum as a source of complement in detecting human blood group antibodies, see P. L. Mollison and Ann R. Thomas, 1959, to be published.) The patient's serum was also tested by Dr. Parkin, who reported that no blood-group antibodies could be found using a series of tests, including the "trypsin-Coombs" test.

Discussion

When transfused red cells undergo complete destruction within 24 hours it is to be expected that an antibody, incompatible with the donor's red cells, will be found in the patient's serum. Fudenberg and Allen (1957) have described some cases in which transfused red cells were rapidly destroyed, with haemoglobinuria in one instance, even though no antibody was demonstrable at the time of transfusion. However, in all these cases antibody was either demonstrated some days after transfusion or was known to have been present some time before transfusion.

A diminished survival of transfused red cells due almost certainly to incompatibility but without demonstrable antibody is now well recognized (Loutit, Mollison, and Young, 1943; Mollison, 1956; Jandl and Greenberg, 1957; Adner and Sjölin, 1957), but in these cases the elimination of the donor's red cells takes some days or weeks.

The present case is remarkable in that such rapid destruction occurred in the absence of a demonstrable antibody.

Summary

A case is described in which the patient repeatedly suffered severe haemolytic reactions after the transfusion of apparently compatible blood. It was demonstrated that the transfused red cells were completely eliminated from the circulation within 24 hours of the transfusion, but all known tests for blood-group antibodies failed to reveal any incompatibility *in vitro*.

We thank Mrs. Crookston (formerly Miss Marie Cutbush) for carrying out most of the serological tests; Dr. Dorothy Parkin for determining the full blood groups of the patient and of one of the donors; and Miss M. D. Snelling for permission to publish clinical details of this case.

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BECLAMIDE IN INTRACTABLE EPILEPSY: A CONTROLLED TRIAL

BY

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Though several powerful anticonvulsants have served to transform the management of patients suffering from major epilepsy, there remain a number of epileptics whose attacks are poorly controlled. In such a group of cases attending an epileptic clinic in Newcastle upon Tyne we decided to try the effect of beclamide ("nydrane"; "hibicon"; N-benzyl-B-chloropropionamide). This promising drug is structurally quite different from the conventional anticonvulsants, and has the additional advantage of being relatively non-toxic in therapeutic doses. Its exact mode of action has not yet been determined.

Several favourable reports have already appeared (Hawkes, 1952; Hoenig *et al.*, 1956; Merlis and Martin, 1956; Robinson, 1957; Sharpe, Dutton, and Mirrey, 1958), and we wish to record here our experiences of a double-blind controlled trial using this remedy.

Clinical Material and Methods

Among the patients attending the epileptic clinic of the Royal Victoria Infirmary at the beginning of the proposed trial (September, 1957) were 16 whose attacks were clearly uncontrolled despite substantial doses of the commoner anticonvulsants in many different combinations. Three of these patients were deemed unsuitable for the trial: the first was pregnant, the second was a psychopathic adolescent girl who was subsequently admitted to a mental hospital, and the third was a mentally defective woman of 34 whose

TABLE I.—*Clinical Details of the Patients in the Trial*

Case No.	Age	Clinical Type of Epilepsy	E.E.G. Findings	Age of Onset (Yrs)	Anticonvulsant Remedies Previously Received					
					PB.	MPB.	Prim.	Acet.	Ph.	Me.
1	44	Post-traumatic	Not done	39	PB.	MPB.	Prim.	—	Ph.	—
2	27	Focal	Temporal lobe spikes	17	,,	,,	,,	—	,,	—
3	38	? Temporal lobe	Normal	27	,,	—	,,	—	,,	—
4	34	Grand mal	Not done	18	,,	—	,,	—	,,	—
5	49	,, ,,	,, ,,	46	,,	—	,,	—	,,	—
6	45	,, ,,	Normal	43	,,	—	—	—	,,	—
7	21	Structural with birth injury	Temporal lobe spikes	11	,,	—	Prim.	Acet.	,,	—
8	39	? Temporal lobe	Synchronous spike and wave	6	,,	—	,,	—	,,	—
9	21	Focal	Parieto-temporal delta activity	10	,,	—	,,	—	,,	—
10	51	Grand mal	Temporal lobe delta activity	43	,,	—	,,	—	,,	—
11	30	Temporal lobe	Temporal lobe spikes	13	,,	—	,,	Acet.	,,	Me.
12	50	,, ,,	,, ,, ,,	41	,,	MPB.	—	—	,,	,,
13	38	,, ,,	Normal	12	,,	—	Prim.	—	,,	—

PB. = Phenobarbitone. MPB. = Methylphenobarbitone. Prim. = Primidone. Acet. = Acetazolamide. Ph. = Phenytoin. Me. = Methoin.

relatives were unreliable. The diagnosis of major or temporal lobe epilepsy in the remaining 13 cases was clearly established on clinical grounds, and confirmatory electroencephalographic evidence was available in the majority of cases. Table I gives brief clinical details of the cases and of the previous treatment they had received. Most of these patients were living active and useful lives despite their attacks, and all attended hospital at monthly intervals for review throughout the trial.

At the outset the purpose of the trial was explained, and each patient agreed to co-operate fully. The anticonvulsants which the patients had been taking immediately before the trial period began were continued throughout. The patients (or responsible relatives) were asked to keep an accurate record of the date and time of epileptic seizures and to note possible side-effects of treatment. All patients were seen and examined at monthly intervals by one of us (J. W.), special attention being paid to the skin, lymph nodes, gums, signs of ataxia, and reflex changes. At the end of each monthly period the patients were questioned about the number of tablets which were left, since from this it was possible to judge whether the medication had been taken regularly. Haematological studies (Hb, W.B.C., differential white count) and urinalysis were carried out at the beginning of the trial, and at each three-monthly stage thereafter.

For a preliminary period of three months the patients were observed on the anticonvulsant regimen they were already taking. During each of the two subsequent three-monthly periods they received either unmarked beclamide tablets in a dosage of 1 g. three times daily or else identical control tablets of lactose, in addition to the drugs they were already receiving. Care was taken to see that the tablets were taken routinely each day at the same times. Neither the patients nor the doctor responsible for assessing the results (J. W.) knew which tablet was being taken at any one time. Tablets were packaged in the hospital dispensary and were administered according to a prearranged plan devised by one of us (D. J. N.).

At the end of this six-monthly period those patients whose attacks were still relatively uncontrolled were observed for a further four to eight weeks while receiving beclamide in a dosage of 4 g. daily in addition to their previous medication.

Results

The two major difficulties encountered in this out-patient trial were (1) maintaining accurate records of attack frequency; and (2) ensuring that patients took their tablets regularly. Judging by the numbers of tablets left at the end of each month it is certain that most patients took the full dose of tablets, whilst the others took at least 90% of the recommended dose. Both difficulties are overcome to a certain extent, however, by conducting a controlled trial, since these imponderables were obviously operating during both test and control periods. We feel, therefore, that the numbers of seizures per patient in each period of the trial as recorded in Table II are reliable for our purpose.

TABLE II.—*Results of Controlled Trial, Showing Numbers of Seizures Occurring During Each Treatment Period*

Case No.	Existing Treatment (Daily Total)	No. of Seizures During Each Period of Trial			
		I	II	III	IV
1	Primidone 1½ g., phenytoin 4½ gr. (0·3 g.) ..	15	14 C	18 + B	4 (4 wks)
2	Primidone 1 g., phenytoin 4½ gr. (0·3 g.), acetaz. 500 mg. ..	237 –	296 + C	153 + B	53 + (4 ,,)
3	Primidone 1 g., phenytoin 6 gr. (0·4 g.) ..	16	11 B	12 C	1 (4 ,,)
4	Phenobarb. 1½ gr. phenytoin 6 gr. (0·4 g.) ..	15	5 C	2 B	0 (8 ,,)
5	Primidone 1½ g., phenytoin 4½ gr. (0·3 g.) ..	45	45 B	29 C	21 (9 ,,)
6	Phenobarb. 1½ gr., phenytoin 3 gr. (0·2 g.) ..	5	7 C	7 B	9 (9 ,,)
7	Primidone 1½ g., acetaz. 500 mg. Phenytoin, 3 gr. (0·2 g.)	95 +	59 + B	120 + C	32 (4 ,,)
8	Primidone 1½ g., phenytoin 4½ gr. (0·3 g.)	9	0 B	0 C	1 (4 ,,)
9	Primidone 1 g., phenytoin, 1½ gr. (0·1 g.) ..	152	107 B	119 C	29 (4 ,,)
10	Phenobarbitone 1 gr., phenytoin 3 gr. (0·2 g.)	6	3 B	8 C	6 (9 ,,)
11	Methoin 300 mg., phenobarb. 3 gr., phenytoin 4½ gr. (0·3 g.)	31	35 C	23 B	14 (8 ,,)
12	Methoin, 200 mg., methylphenob. 3 gr., phenytoin 3 gr. (0·2 g.) ..	33	11 C	12 B	—
13	Primidone 750 mg., phenytoin 3 gr. (0·2 g.)	5	8 C	3 B	—

Period I = Preliminary three months observation period. Period II = First three months of controlled trial: 3 g. day of beclamide or lactose in divided doses. Period III = Second three months of controlled trial: 3 g./day of beclamide or lactose in divided doses. Period IV = Further period (stated): 4 g./day in divided doses. B = Beclamide. C = Control.

Clearly there is a great deal of variability in the results, and in some of the patients who had large numbers of fits it was impossible to obtain an accurate figure.

In these circumstances the method of transforming the observations into *log* (number of fits + 1) was used to produce normal variables to which standard statistical tests can be applied (Quenouille, 1950). There is some justification for using a logarithmic transformation of the number of fits, in so far as a successful treatment might be expected to reduce the number of fits by a constant *proportion*—for example, to half the number suffered without the treatment—rather than by a constant *number* of fits per three-monthly period. Thus a

constant change in the logarithm of the number of fits is the desired effect of a treatment. The addition of 1 to the number of fits before taking logarithms is necessitated by the fact that in a few patients 0 fits were recorded in a period. In this section of the report, *log* (number of fits +1) in a particular period and for a particular patient is referred to as the score.

Comparison of Beclamide with the Control (Periods II and III)

The effect of beclamide in each patient was measured by subtracting the score for the control from the score for beclamide. In the 13 patients these varied from +0.18 to −0.35, with an average of −0.118. This figure is significantly different from zero ($t=2.32$, d.f.=12, $P<0.05$). Translating back from logarithms, this means that beclamide reduces fits to about 75% of the figure with the control tablets. When on beclamide three of the patients had more attacks, two had the same number, and eight had fewer.

The 13 patients were divided as equally as possible into groups receiving beclamide in the second period and in the third period, there being six in the first group and seven in the second. Allocation to these groups was made by random selection before the trial began.

The second and third periods coincided with the snowy winter of 1957–8 and the wet spring of 1958. To investigate the possible effect of season on the frequency of seizures a comparison of the scores in the second and third periods (regardless of the treatment given) was made. The average difference between scores was only 0.033, which is not significant ($t=0.55$, d.f.=12, $P=0.60$).

Effect of the "Control" Tablet

Having thus established that there was no intrinsic difference between the second and third consecutive periods themselves, we were able to compare the scores in these periods with those in the first (observation) period. Comparison of the results in the first period with the same patient's control period in the second or the third period shows that seven patients had fewer fits with the control tablets than with no additional tablet, but the other six had more fits. Thus there is no significant difference between the dummy tablets and observation, and possible psychological effects of an inert tablet can be discounted in this trial. (Comparison of scores between first and control periods yields the same result: $t=1.40$, d.f.=12, $P=0.20$—not significant).

Effect of Increased Dosage of Beclamide

The effect of increasing the dosage of beclamide to 4 g. a day was tested more briefly in 11 patients at the end of the third period. While it is not recommended that a further period should be added to a balanced design, we feel that the similarity between results in the second and third periods to some extent justifies comparisons between the results in this fourth period and those in previous ones. The shorter periods used make the test rather less sensitive than those in the main part of the trial.

For comparison, the numbers of fits recorded in four, eight, or nine weeks were increased proportionately to give the corresponding figures for 12 weeks (as in periods II and III). Six of the 11 patients had proportionately more fits than in the period in which they were receiving beclamide in the dosage of 3 g. a day. The average difference between the scores was only 0.01, giving no evidence at all in favour of the higher dosage. However, the variability in results was greater, and the 95% confidence limits for the average difference in scores are from −0.21 to +0.19, meaning that the higher dosage could in the long run reduce fits to 60% or increase them to 162% within the limits of the data here recorded.

Side-effects

Several patients attributed occasional nausea and anorexia to the tablets, but these symptoms can be discounted because they occurred just as often with the supposedly inert controls. The size of the tablets (0.5 g.) caused difficulty in a minority of patients. The drug was never incriminated as a cause of skin rash, gum hypertrophy, or any neurological abnormalities. Depression or somnolence was not observed as an indubitable effect of the tablets; neither was a specific euphoriant effect detected, apart from the optimism arising from better control of seizures in certain patients.

Four patients developed a mild hypochromic anaemia over the course of the whole trial period, but we were able to attribute this in all cases to blood loss (haemorrhoids, menstruation, etc.) or to poor diet. One patient (Case 7) developed a severe macrocytic anaemia (Hb, 8.25 g. per 100 ml.) which responded rapidly and completely to oral folic acid; he was already having large doses of phenytoin and primidone, and it seems probable that these drugs and not the beclamide were responsible for the anaemia.

Albuminuria and reducing substances in the urine were not detected in any case.

Discussion

As in trials previously reported, beclamide was found to exert a significant though not strikingly beneficial effect when given in divided doses of 3–4 g. a day in poorly controlled epileptics. Nine out of 13 patients were improved, with a reduction in the overall frequency of seizures to 75% of the previous figure. Our observation did not suggest any difference in the efficiency of the drug in apparent "idiopathic" epilepsy on the one hand, or in focal or temporal lobe epilepsy on the other. We did not use this remedy in cases of petit mal. Compared weight for weight with the commonly used anticonvulsants, beclamide is not a powerful agent, but it has the singularly valuable property of being non-toxic in therapeutic doses. Our observations tend to confirm the non-toxicity of the drug, though it must be emphasized that a longer trial than ours would be necessary to exclude toxic effects.

Initial leucopenia and the transient appearance of a reducing agent in the urine have been reported by other workers, but these changes were never observed in our cases, possibly because haematological studies and urinalysis were carried out only at three-monthly intervals.

We believe that beclamide has a place in the management of major or temporal lobe epilepsy, but its relative lack of efficiency as an anticonvulsant, together with the large size of the tablets, which makes them unsuitable for children, as well as their price (currently £18 per 1,000 tablets, compared with £6 4s. per 1,000 tablets for primidone, the most expensive of the anticonvulsants in common use), will limit the use of this drug to epileptics whose fits are poorly controlled by phenobarbitone, phenytoin, or primidone, or for whom these drugs are too toxic.

Summary

In a statistically controlled double-blind trial of beclamide in 13 patients suffering from uncontrolled major or temporal lobe epilepsy it was shown that that drug, in a dosage of 3 g. daily, was significantly more efficient than an inert tablet, reducing the number of seizures to 75% of their previous frequency without any noteworthy side-effects. Control (inert) tablets were shown not to have any psychological placebo effect. Little improvement occurred on increasing the dosage of beclamide from 3 g. to 4 g. a day, but this increased dosage was given for a relatively short period and the evidence on this point is inconclusive.

It is concluded that beclamide has a significant anticonvulsant effect, but in view of the high cost of this remedy it should be used only in epileptic patients who have failed to respond to other remedies. It appears that the drug may safely be given in combination with other anticonvulsants.

We thank Dr. H. G. Miller for allowing us to include in the trial patients who were under his care; Miss Garnett, chief pharmacist, Royal Victorial Infirmary, for her co-operation in arranging the double-blind controlled trial; and Dr. S. Phillips and Rona Laboratories Ltd. for supplying the beclamide and identical control tablets.

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RENAL FAILURE IN HYPERCALCAEMIC SARCOIDOSIS

BY

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Hypercalcaemic sarcoidosis is associated in many cases with renal failure. Sarcoid granulomatous infiltration of the kidneys is not uncommon, but the lesion is usually focal and not extensive. Berger and Relman (1955) reported a case of sarcoidosis and renal insufficiency showing granulomatous infiltration of the kidneys without nephrocalcinosis or associated renal disease. Other diseases, such as pyelonephritis (Dent *et al.*, 1953) and renal tuberculosis (Longcope and Freiman, 1952), may be present to account for renal insufficiency in patients with disseminated sarcoidosis. Klatskin and Gordon (1953) suggested that renal failure in sarcoidosis may be due to hypercalcaemia and nephrocalcinosis. The association of nephrocalcinosis and renal failure in hypercalcaemic sarcoidosis has been reported (Longcope and Freiman, 1952; Shulman *et al.*, 1952; Davidson *et al.*, 1954; Scholz and Keating, 1956). In addition, steroid therapy has been followed by reduction of the hypercalcaemia and improvement in renal function (Shulman *et al.*, 1952; Dent *et al.*, 1953; Gleckler, 1956; Phillips and Fitzpatrick, 1956; Scholz *et al.*, 1957). We report a case of hypercalcaemic sarcoidosis with renal failure. Steroid therapy resulted in improvement in renal function, although serial renal biopsies showed persistence of nephrocalcinosis.

Case Report

A 36-year-old man was admitted to hospital on April 21, 1958. He complained of weakness, polyuria, polydipsia, insomnia, and exertional dyspnoea, gradually increasing over two years. The past medical history revealed that in 1947 he developed a polyarthritis which responded poorly to salicylates. In 1953 a pulmonary lesion was detected by *x*-ray examination, and on the basis of follow-up radiological and sputum studies a diagnosis of sarcoidosis was made. He had no history of excessive intake of milk, alkalis, or vitamin D.

The physical examination revealed an asthenic, sallow man. There were no skin lesions. Band keratitis was absent. The blood pressure was 140/90 mm. Hg; pulse rate 80 a minute; temperature 98.6° F. (37° C.); respirations 22 a minute. There was enlargement of the spleen to 4 cm. below the left costal margin.

Laboratory examination showed a blood haemoglobin of 10.5 g./100 ml., and white-cell count of 5,000/c.mm., with a normal cell distribution. The sedimentation rate was 20 mm./hour (normal 2–6 mm./hour). Red-cell indices showed a normochromic normocytic anaemia, and the direct Coombs test was negative. The specific gravity of the urine was 1,010 and the daily urine volumes averaged 2,800 ml. Water deprivation did not correct the isosthenuric polyuria. There was no proteinuria, cylinduria, haematuria, or pyuria. Urine was sterile on culture. Mantoux reaction 1:1,000 was negative. X-ray examination of the chest revealed diffuse fibrosis scattered throughout both pulmonary fields. *X*-ray studies of the hands, feet, and spine showed no abnormality. A plain *x*-ray film of the abdomen disclosed a small calculus in the lower pole of the right kidney. An intravenous pyelogram showed poor dye excretion by both kidneys. Renal tomography did not demonstrate calcinosis. The kidneys appeared normal in size and position. An electrocardiogram was normal. The blood urea was 93 mg./100 ml. Serum calcium was 13.2 mg./100 ml.; serum phosphorus, 4 mg./100 ml.; serum alkaline phosphatase, 8 King–Armstrong units; total protein, 7.7 g./100 ml. (serum albumin 4.3 g., serum globulin 3.4 g.); electrophoretic pattern showed an increase in gamma-globulin; serum bilirubin, 0.2 mg./100 ml.; thymol turbidity, 0.5 unit; zinc sulphate, 5.8 units; blood cholesterol, 58 mg./100 ml.

A left aspiration renal biopsy (Fig. 1) was performed by one of us (D. J. D.) with a Franklin modification of the

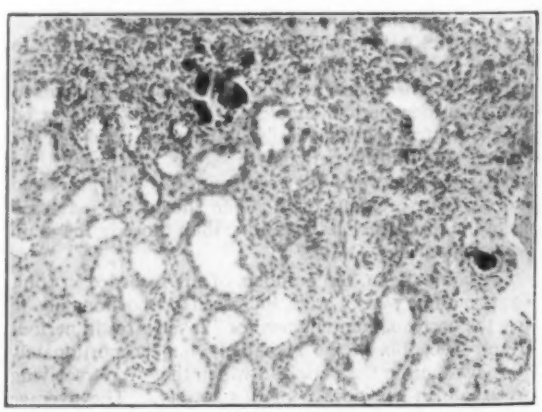

FIG. 1.—Renal biopsy before commencement of cortisone. Nephrocalcinosis with increase in interstitial connective tissue and cellular infiltration. (Haematoxylin and eosin. ×103.)

Vim–Silverman needle. The tissue contained 22 glomeruli. Nephrocalcinosis was present; five glomeruli were fibrosed, and the others appeared normal. There were patches of fibrous tissue with inflammatory cell infiltration which could be related to the calcinosis or represent the stigmata of chronic pyelonephritis. No sarcoid granulomatous infiltration was seen.

The patient was treated with cortisone, 300 mg. the first day, 200 mg. the second day, and 100 mg. the third and subsequent days. One month after treatment the blood urea was 42 mg./100 ml., and the serum calcium 11.2 mg./100 ml. (Fig. 2). The urine had a specific gravity of 1,018. There was no polyuria. A water-concentration test demonstrated normal renal concentrating ability. A left aspiration renal biopsy was then repeated. The tissue contained 10 glomeruli (Fig. 3). There was no change in the histological features or in the severity of the nephrocalcinosis.

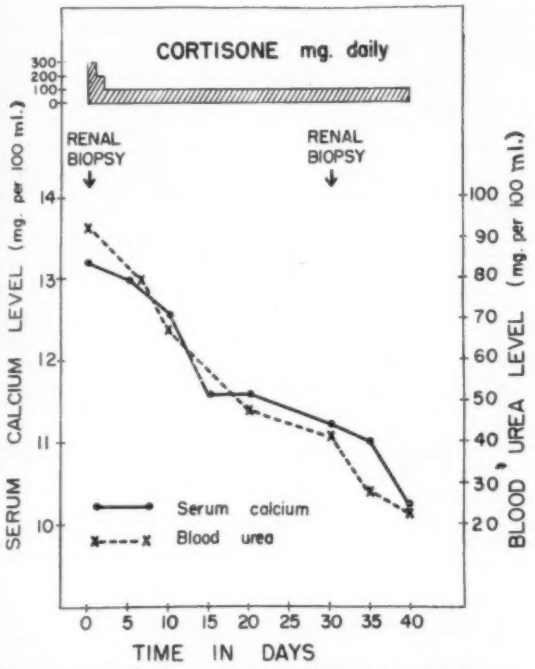

FIG. 2.—Levels of serum calcium and blood urea after treatment with cortisone.

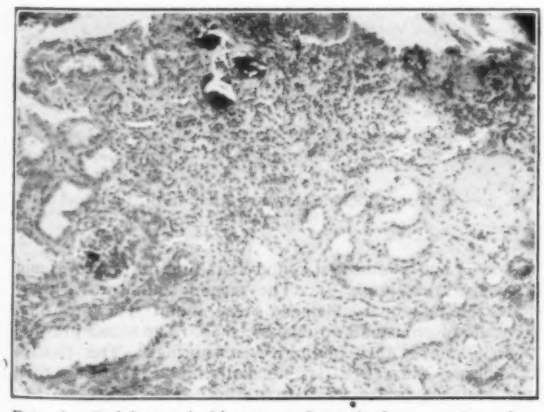

FIG. 3.—Serial renal biopsy performed four weeks after commencement of cortisone. There is no change in the histological severity of nephrocalcinosis. (Haematoxylin and eosin. ×75.)

C

Discussion

Hypercalcaemia occurs in 20% of cases of sarcoidosis (Longcope and Freiman, 1952), but the mechanism is uncertain. Recent studies have demonstrated a disturbance of metabolism in sarcoidosis characterized by an excessive alimentary absorption of calcium (Henneman *et al.*, 1954; Anderson *et al.*, 1954; Scholz *et al.*, 1957). Increased absorption of calcium from the gut may be due to an abnormal sensitivity to endogenous vitamin D (Anderson *et al.*, 1954) or to excessive production of a vitamin-D-like substance (Henneman *et al.*, 1954). Cortisone has been shown to correct this disturbance of calcium metabolism. Following cortisone administration there is increased faecal excretion of calcium associated with a decrease in its urinary excretion and a return of the serum level to normal limits (Anderson *et al.*, 1954; Henneman *et al.*, 1956; Scholz *et al.*, 1957).

The effect of hypercalcaemia on the kidney is the production of nephrocalcinosis and renal insufficiency. Both the duration and the severity of the hypercalcaemia determine the presence and degree of renal calcinosis. This patient had a serum calcium level of 13.2 mg./100 ml. Evidence of renal insufficiency was present, with a blood urea of 93 mg./100 ml. Renal biopsy showed nephrocalcinosis with areas of interstitial fibrosis.

The renal failure that follows nephrocalcinosis differs from that due to the more common types of renal disease (Elsom *et al.*, 1936). Proteinuria, haematuria, cylinduria, and hypertension are unusual in nephrocalcinosis. More commonly found are inordinate weakness, polyuria, polydipsia, and azotaemia. This patient complained of weakness, anorexia, and polyuria. These symptoms may be explained either by hypercalcaemia or by renal insufficiency. Changes of chronic pyelonephritis may be observed in the kidneys at necropsy in patients with nephrocalcinosis. Biopsy of the renal tissue of this patient showed a number of obliterated and fibrosed glomeruli, with areas of fibrous tissue and inflammatory cell infiltration. Whether these changes are a consequence of calcinosis or evidence of chronic pyelonephritis cannot be determined from renal biopsy tissue.

Renal insufficiency in cases of sarcoidosis is commonly ascribed to hypercalcaemia with nephrocalcinosis, without, however, adequate biochemical, radiological, or histological evidence. In a case of sarcoidosis with renal failure and hypercalcaemia, Longcope and Freiman (1952) described the renal lesion found at necropsy as pyelonephritis secondary to nephrolithiasis and nephrocalcinosis. Davidson *et al.* (1954) reported seven cases of nephrocalcinosis with hypercalcaemia due to sarcoidosis. In two cases renal insufficiency was present and nephrocalcinosis was confirmed at necropsy. Shulman *et al.* (1952) found three cases of renal insufficiency with hypercalcaemia in sarcoidosis. In one case nephrocalcinosis was present at necropsy. In the present case radiological examination of the kidneys, including tomography, failed to reveal calcinosis, which was, however, demonstrated by means of aspiration renal biopsy.

Steroid administration in hypercalcaemic sarcoidosis has been shown to result in improved renal function (Shulman *et al.*, 1952; Dent *et al.*, 1953; Gleckler, 1956; Phillips and Fitzpatrick, 1956; Scholz *et al.*, 1957). Phillips and Fitzpatrick (1956) postulated renal calcinosis in those patients in whom improvement was

slow and imperfect after correction of the hypercalcaemia by cortisone. The present case report shows that, in spite of established renal calcinosis, marked and rapid improvement in renal function followed the use of cortisone. There was no change in the degree of renal calcinosis as determined by serial renal biopsy after one month of cortisone therapy, although renal function had returned to normal. The mechanism is therefore unlikely to be the removal of precipitated calcium from the kidney, although this may well be the end-result of continued steroid administration. We suggest that cortisone exerts its beneficial effect on the renal failure of hypercalcaemic sarcoidosis principally by correcting the hypercalcaemia itself.

Summary

A case is reported of sarcoidosis with hypercalcaemia, nephrocalcinosis, nephrolithiasis, and renal failure. Treatment with cortisone resulted in lowering of the serum calcium level to normal and improvement in renal function within one month, although serial renal biopsies showed no change in the degree of nephrocalcinosis during this time.

It is suggested that renal failure in hypercalcaemic sarcoidosis is not necessarily a reflection of irreversible nephron destruction by calcinosis, but that it may result from the high level of circulating calcium itself adversely affecting renal function. Also, the presence of nephrocalcinosis does not necessarily imply that the response to steroid therapy will be unsatisfactory.

We thank Dr. W. Freeborn, general medical superintendent of the Royal North Shore Hospital of Sydney, for allowing us to publish details of this case, and Dr. C. Graham for giving the histopathological report.

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The term "biophysics" has hardly yet had time to acquire a fixed or generally accepted meaning. In consequence, the author of *Elements of Biophysics*, James E. Randall, Ph.D. (of Missouri University), explains that he wrote his book "to present to the student of biology and medicine the physical and quantitative concepts of basic importance to these fields." The subjects he discusses include the following: principles of measurement and statistical analysis: mechanics and kinetics; electricity, atomic structure, and radioactivity. The book has 333 pages and is published by Year Book Publishers for $8.

COR TRIATRIATUM (STENOSIS OF THE COMMON PULMONARY VEIN)

SUCCESSFUL TREATMENT OF A CASE

BY

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In the cor triatriatum the left atrium is divided by a septum into two chambers—postero-superior, which receives the pulmonary veins, and antero-inferior, which opens into the mitral valve and left ventricle. The septum contains one or more apertures which may be large or small, or it may be imperforate, in which case the infant is stillborn or dies in the first few months. Since the septum causes an obstruction at left atrial level, it can simulate the symptoms, radiological appearances, and haemodynamics of mitral stenosis. It is eminently suitable for surgical treatment, yet to date only three successful cases have been reported. A fourth is now presented.

Case Report

A woman aged 28 complained of progressive breathlessness, palpitation, and tiredness for four years. A "leaky valve" had been diagnosed when she was aged 12. Walking a few yards caused severe dyspnoea, but she complained little and was working as a secretary. Orthopnoea, haemoptysis, syncope, or chest pain was not present.

The rhythm was atrial fibrillation; venous pressure was raised to 4 cm. above the sternal angle, and there was an obvious systolic lift to the left of the sternum. The main auscultatory findings were a mitral pansystolic murmur

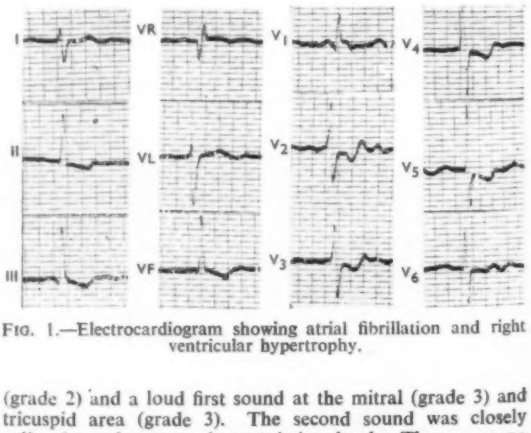

FIG. 1.—Electrocardiogram showing atrial fibrillation and right ventricular hypertrophy.

(grade 2) and a loud first sound at the mitral (grade 3) and tricuspid area (grade 3). The second sound was closely split, the pulmonary element being loud. There was no diastolic murmur and no opening snap. The blood pressure was 120/85. Other findings were normal. The electrocardiogram showed atrial fibrillation and a strong right ventricular hypertrophy pattern (Fig. 1). The heart was moderately increased in size (Fig. 2), the pulmonary artery prominent, and the left atrium slightly enlarged when viewed

in the right oblique position. The lungs showed pulmonary venous congestion with Kerley's lines at both bases. The provisional diagnosis was severe mitral stenosis. Cardiac catheterization was attempted twice, the second time in the semi-recumbent position, but on each occasion the patient developed a rapid ventricular rate and pulmonary oedema before any observations were made.

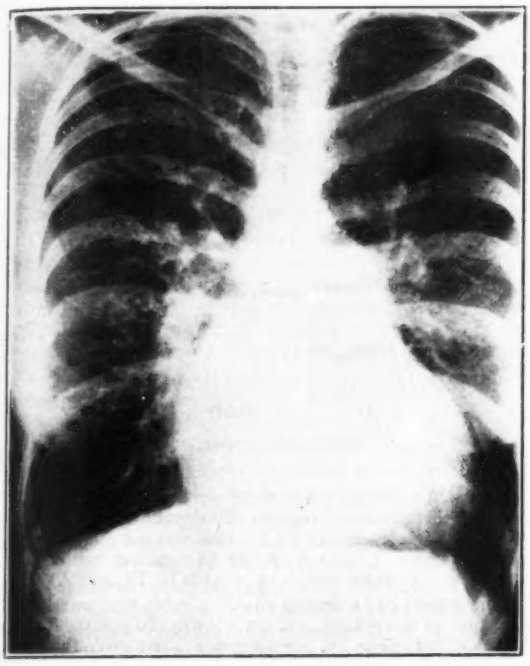

FIG. 2.—*X*-ray film showing cardiac enlargement, prominent pulmonary artery, and hilar vascular shadows. The aortic knob is small. Kerley's lines were present, but are not seen in this reproduction.

At operation the anterior part of the left atrium was soft, but the posterior part, into which the pulmonary veins drained, was tense. The atrium was explored through the appendage; there was moderate mitral incompetence but no stenosis, and the valve cusps were soft and freely mobile. The tense intra-atrial septum was easily palpable and contained a calcified orifice 2 mm. across on the postero-lateral aspect just in front of the pulmonary veins. The septum was divided with a Brock posterior commissure knife from side to side of the atrium. There was an immediate inrush of blood, and a fall in tension in the posterior chamber. No attempt was made to enlarge the orifice in the septum as it was so eccentrically placed.

Mean pressure readings taken at operation were as follows:

	Before	After
Pulmonary artery ..	66 mm. Hg	50 mm. Hg
Third atrium	40 ,,	8 ,,
Left atrium proper ..	8 ,,	8 ,,

Convalescence was normal. Four months later she had no symptoms. The venous pressure was now normal, but atrial fibrillation and the mitral systolic murmur persisted. Cardiac catheterization while she was lying flat gave the following results: pulmonary capillary venous (or left atrial) mean pressure, 5 mm. Hg; pulmonary artery, 35/15 (mean 24) mm. Hg; right ventricle, 35/–3 mm. Hg; cardiac output, 5.2 litres a minute; pulmonary vascular resistance, 4 units (320 dynes sec./cm.^{5}).

Discussion

The first complete anatomical description of the cor triatriatum was given by Church (1868), although passing reference was made to it by Andral (1829). Twenty-nine cases have now been described, including the present one, 20 of these from the literature being well documented by Pedersen and Therkelsen (1954). Individual cases have been reported by Doxiadis and Emery (1953), Becu *et al.* (1955), Hartmann (1955), Lewis *et al.* (1956), Barrett and Hickie (1957), and Keith *et al.* (1958, 2 cases). Incomplete septa and fibrous bands running across the left atrium belong to a different and larger group and are not considered here. Three cases have been operated on successfully—a woman aged 21 (Vineberg and Gialloreto, 1956), a man aged 23 (Lewis *et al.*, 1956), and a girl aged 17 (Barrett and Hickie, 1957).

The clinical picture based on the present case and others of comparable severity described in the literature appears in a child or young adult. The chief complaint is breathlessness; paroxysmal dyspnoea is uncommon. The rhythm is sinus or atrial fibrillation. The diagnosis of severe mitral valve disease is suggested by a mitral pansystolic murmur, a loud mitral first sound, and signs of pulmonary hypertension with or without pulmonary incompetence, and is supported by the electrocardiogram and cardiac catheterization. This diagnosis is made uncertain by the absence of a mitral diastolic murmur and opening snap and little or no left atrial enlargement radiologically. The possibility of a left atrial myxoma is usually raised. In all the cases to date, however, the diagnosis of cor triatriatum has been made only after exploratory cardiotomy.

The aperture in the septum varies in size from a few millimetres to 2 cm. across, and its edges may be calcified. It is usually centrally placed, but may be close to the periphery. Sometimes two or more apertures are present. The foramen ovale is in the superior chamber and may be open or closed. The left atrial appendage is part of the inferior chamber, where the pressure is low and is therefore not seen on the straight *x*-ray film of the heart. The mitral valve is usually normal, but may be hypoplastic with shortened chordae (Parsons, 1950) or deformed, allowing slight regurgitation as in Vineberg and Gialloreto's case and the present case. One instance of a tricuspid valve with two fused leaflets has been reported (Barnes and Finlay, 1952). The commonest associated congenital defects are a ductus arteriosus (three cases) and Fallot's tetralogy (two cases).

The embryological derivation of the cor triatriatum has been debated for more than 70 years. Kingston Fowler's (1882) contention that the anomalous septum was the septum primum and the aperture the interatrial ostium primum was preferred by Wardrop Griffith (1902) to his own thesis of failure of amalgamation of the common pulmonary vein in the left atrium. The latter theory has come to be generally accepted to-day, and certain authors feel so strongly about it that they call the condition "congenital stenosis of the common pulmonary vein" (Edwards *et al.*, 1951).

Summary

A woman aged 28 suspected of having mitral stenosis was found at operation to have a cor triatriatum. The

anomalous intra-atrial septum was successfully divided. The pressure in the third atrium fell immediately from 40 to 8mm. Hg. This is the fourth case in the literature to be treated successfully by surgery.

We are indebted to Dr. K. P. Ball, Central Middlesex Hospital, who referred the patient to us.

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Medical Memoranda

Myocardial Infarction in a Young Adult

In the last two decades it has become apparent that coronary artery disease does occur in young adults. Newman (1946) published a series of 50 cases, the youngest aged 20. Poe (1947) showed that in 280 unselected necropsies on American Service personnel between the ages of 18 and 40, coronary thrombosis was the cause of death in 3.2%.

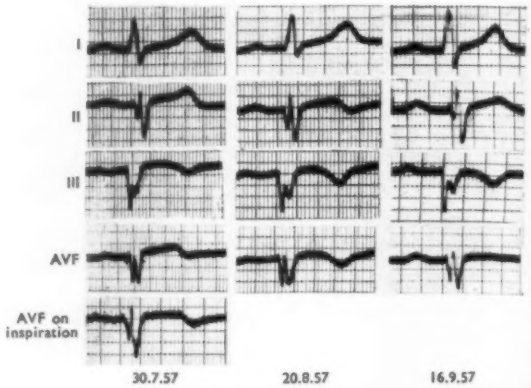
CASE REPORT

A well-developed athletic young man aged 19, on holiday from Germany, attended the casualty department on July 27, 1957, having been awakened early that morning by a constant gripping substernal pain, radiating to both shoulders and made worse by deep breathing. He had no cough, no sputum, no haemoptysis, and no dyspnoea. The pain lasted for two hours. The previous day he had felt unwell after strenuous exercise. His past history included several attacks of tonsillitis, the last occurring several weeks previously. A routine medical examination, including an electrocardiogram the year before, had been normal. His mother had angina pectoris, and his father had had a myocardial infarct.

On examination, his temperature was 99° F. (37.2° C.). His tonsils were enlarged and inflamed, and large tender tonsillar glands were palpable. His pulse rate was 64, and regular. His blood pressure was 110/50, and there were no cardiac murmurs or signs of cardiac failure. The other systems were normal.

Investigations.—Haemoglobin, 99%; W.B.C., 5,000 (polymorphs 51%, eosinophils 5%)→8,000 (polymorphs 67%, eosinophils 12%)→5,000 (polymorphs 54%, eosinophils 4%). E.S.R., 13→6 mm. (Wintrobe). W.R. and Kahn test negative. Chest *x*-ray examination normal. Serum transaminase, 29 units; two weeks later it was 12 units. C-reactive protein, negative. Blood cholesterol, 174 mg./100 ml. Throat swab showed *Streptococcus viridans*. 120 units of antistreptolysin per ml. No L.E. cells. Urine normal. Electrophoretic strip, moderate increase in γ-globulin; normal pattern 10 days later. Stools: no parasites or cysts.

An electrocardiogram on admission suggested a recent posterior infarction, with elevated ST segment in standard leads II and III, and Q waves in leads II, III, and AVF (on inspiration). Chest leads were normal. Serial records showed that T-wave inversion developed in lead II four days after admission (see Fig.). This was not present in the final tracing. Elevation of the ST segment settled over six weeks. Q waves remained in leads II, III, and AVF.



Serial electrocardiograms

The patient had a second attack of substernal pain lasting an hour, 48 hours later, and ran a low-grade pyrexia for two weeks. Otherwise his convalescence was uneventful. His blood pressure rose to 140/80. After 10 days he developed an apical systolic murmur and a split A 2, which were still present on his discharge on September 19.

COMMENT

This case shows various features which have been observed in previous series. Coronary artery disease in young people is very much commoner in men than in women (30:1), and occurs in a mesomorphic type of build (Gertler *et al.*, 1951). A family history of ischaemic heart disease can be demonstrated four times more frequently than in a control group. The attack is often related to effort, and in 50% of the cases there are premonitory feelings, which at the time or in retrospect can be attributed to myocardial ischaemia (Yater *et al.*, 1948). This patient complained that the pain increased on breathing deeply, although there was no pleural or pericardial rub, a symptom which was noted in 10% of the cases of Yater *et al.*

We thank Dr. H. V. Morlock, Dr. F. V. Gardner, and Dr. E. M. Spence for their help and encouragement, and Dr. H. V. Morlock for permission to report this case.

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Reviews

OESOPHAGUS IN MOTION

An Atlas of Esophageal Motility in Health and Disease. By Charles F. Code, M.D., Ph.D., Brian Creamer, M.D., M.R.C.P.(Lond.), Jerry F. Schlegel, B.S., Arthur M. Olsen, M.D., M.S., F. Edmund Donoghue, M.D., M.S., and Howard A. Andersen, M.D., M.S. (Pp. 134+ix. 63s.) Springfield, Illinois: Charles C. Thomas. London: Blackwell Scientific Publications. 1958.

This book from the Mayo Clinic gives an account of work carried out there during the past seven years on normal and abnormal motor activity of the oesophagus in man. It provides a pictorial record of these investigations with a minimum of descriptive writing. It is a very good example of the visual method of teaching, though it is hardly fair to describe, as the publishers have done, the written word as a background pattern against superimposed illustrative material. The result is certainly a remarkably clear and easily understandable account of oesophageal movements, in both health and disease.

The recordings of motility were done by the use of tiny electromagnetic pressure transducers, about 1 cm. in length, which after being swallowed transmit pressure changes to a galvanometer and thence by a reflecting mirror to a camera lens. The physiological studies given show the peristaltic contraction of the oesophagus in deglutition with early relaxation of the gastro-oesophageal sphincter, followed by a more prolonged sphincter-contraction at the end of swallowing. In patients with achalasia peristalsis is absent with complete motor inactivity of the oesophagus; dilatation and failure of the gastro-oesophageal sphincter to relax develop in severe cases. Two other conditions investigated are diffuse spasm of the oesophagus and scleroderma. In the former prolonged and abnormal contractions of the oesophagus occur with extremely high pressures, though levels as high as 500 cm. of water were recorded without complaint of pain. The incoordinated motor activity of diffuse oesophageal spasm is a condition the aetiology of which is little known, though the syndrome of intermittent dysphagia and substernal pain is well recognized.

This atlas is an interesting and useful work on an important subject; it should stimulate clinicians to observe and record the symptomatology of the oesophagus, which has only in recent years begun to receive the attention it deserves.

THOMAS HUNT.

PSYCHOLOGICAL TESTS

Diagnostic Performance Tests. A Manual for Use with Adults. By Boris Semeonoff and Eric Trist. Foreword by P. E. Vernon. (Pp. 176+xv. 32s.) London: Tavistock Publications Ltd. 1958.

The earlier psychologists who were responsible for introducing or advocating the use of standardized tests regarded them primarily as an adjunct to the older methods of clinical case-study. Unfortunately, during the last 20 years or so the two complementary procedures have tended to fall into separate hands, and even to be treated as rival techniques, each criticizing the other for its obvious limitations. The authors of this new contribution to diagnostic testing insist emphatically on the need for both types of approach: and have made an earnest endeavour to bring together both quantitative and qualitative methods in a single composite procedure which will be (so they hope) "at once flexible and rigorous."

The chief purpose of their book is to provide instructions for the use of five standardized performance tests, some entirely new, others based on well-established devices, and the whole forming a valuable scheme for assessing the mental efficiency of adults. Most of the work on which their battery is based was carried out during the recent war, first at Mill Hill Emergency Hospital, and then at various War Office Selection Boards. A number of supplementary tests, chiefly of a verbal type, together with illustrative case-material, are described in a series of appendices. The concluding chapters supply tables of norms and a method for converting the raw test scores into "intelligence gradings."

Unfortunately, for reasons of security, the documents relating to the subsequent histories of the individuals tested could not be made accessible to the writers. Consequently no detailed evidence can as yet be offered to demonstrate the validity of the assessments or of the interpretation suggested for the different types of behaviour observed during the actual testing. Nevertheless the authors' conclusions rest on a vast amount of accumulated experience; and the book as a whole forms a welcome addition to the methods available for exploring adult personality and assessing adult intelligence.

CYRIL BURT.

CLINICAL CHEMISTRY

Clinical Chemistry in Practical Medicine. By C. P. Stewart, D.Sc.(Dunelm.), Ph.D.(Edin.), and D. M. Dunlop, B.A. (Oxon.), M.D., F.R.C.P.(Edin.), F.R.C.P.(Lond.). Fifth edition. (Pp. 342+vii; illustrated. 27s. 6d.) Edinburgh and London: E. and S. Livingstone, Ltd. 1958.

The appearance of a third post-war edition of this book is a sufficient indication of its popularity and evidently indicates a continuing market for the type of information provided. The arrangement of this edition follows closely that of the last, but the book is now some 20 pages longer. The chapters are arranged on a biochemical rather than a pathological basis, and this makes it somewhat difficult to look up all the metabolic abnormalities in any one disease. The addition of a table of changes in the various diseases would have been useful here, though the revised index is of some help in this connexion. The greatest modification is seen in the last chapter, in which "Nutritional Deficiencies" has become "Miscellaneous Metabolic Abnormalities" and which now covers a wider field. This is an important improvement, and includes sections on aminoaciduria, haemochromatosis, inborn errors of metabolism, etc.

The book is well written and produced, and most chemical tests of value find a place. The discussion of these procedures is excellent. Detailed instructions are not given except for an appendix in which a few of the simpler tests are described. In view of this and for other reasons the absence of any references to other works or to original papers is to be regretted. No doubt the authors had good reasons for adopting this policy, but one would have preferred to find at least some references, particularly when various authorities are quoted by name without even initials to assist the uninitiated in their identification.

The book will undoubtedly be valuable to a wide range of readers, including senior medical students.

practitioners, and junior hospital staff. As stated in the preface, it is not intended primarily for laboratory workers, although many will no doubt consult it, if only to anticipate the requests of their clinical colleagues. It provides a very useful bridge between the wards and the biochemical laboratory, and should make an important contribution to their mutual co-operation.

N. F. MACLAGAN.

OPHTHALMIC PHOTOGRAPHY

A System of Ophthalmic Illustration. By Peter Hansell, M.R.C.S., F.R.P.S., F.B.P.A. (Pp. 114+xi; illustrated. 43s.) Springfield, Illinois: Charles C. Thomas. Oxford: Blackwell Scientific Publications. 1958.

Illustrations are particularly valuable in ophthalmology, where so much depends on inspection; and since the inspection of ocular signs calls for specialized techniques the difficulties of presenting illustrations of such signs are not inconsiderable. For this reason hand drawings of fundus appearances are still better than photographs, even when taken by the latest special camera. For the more superficial parts of the eye photography has proved highly successful, and particularly advantageous when stereoscopic views can be obtained.

Dr. Peter Hansell's book is an excellent guide to the problems of photography in relation to ophthalmology. The technical aspects are discussed fully, and clear indications are given of the procedures advocated. A useful chapter deals with motion-picture photography, and even experts will find much that is helpful in the chapter on special techniques. Indicative of the fullness of the text are the sections dealing with photography of operations and with appearances as seen with the slit-lamp. As befits a book of this type, the illustrations are both copious and excellent. More information on hand drawing would be welcome in a second edition.

ARNOLD SORSBY.

ANTI-TUBERCULOSIS CAMPAIGN IN GLASGOW

Glasgow's X-ray Campaign Against Tuberculosis. 11th March–12th April, 1957. (Pp. 117; illustrated. 5s.) Glasgow: Corporation of Glasgow. 1958.

This report is concerned mainly with the organization for the very successful campaign to examine by chest radiography as many as possible of the adult citizens of Glasgow in the spring of 1957. Its interest lies in the description of the detailed planning that was undertaken in advance, of the publicity methods, and of the arrangements for maintaining a very high rate of working throughout—that is, five weeks of constant *x*-raying. It is therefore essential reading for anyone planning a similar campaign in a large urban area, but it is as yet difficult to judge from the results whether all large cities should make similar endeavours. Certainly nothing less than the 76% of residents *x*-rayed in Glasgow could now be accepted as adequate. More than 2,200 cases of active tuberculosis in Glasgow residents were discovered in the five-week campaign—rather more than the total of notifications for the year 1956. There can be no doubt of the value of discovery on this scale, but the greatest importance of such campaigns lies in their ability to break the chain of infection and thereby to prevent cases from developing, and this can be satisfactorily demonstrated only over the years to come.

V. H. SPRINGETT.

BOOKS RECEIVED

Review is not precluded by notice here of books recently received.

A Text-Book of Bacteriology. By R. W. Fairbrother, T.D., M.D., D.Sc.(Man.), F.R.C.P.(Lond.). Eighth edition. (Pp. 502+viii; illustrated. 25s.) London: William Heinemann, Medical Books, Ltd. 1959.

Blood Pressure Sounds and their Meanings. Part 2. ***Aetiology of Melanotic Cancer.*** By John Erskine Malcolm, B.Sc., M.B., Ch.B., F.R.C.S. (Pp. 70+vii; illustrated. 12s. 6d.) London: William Heinemann, Medical Books, Ltd. 1959.

The Medical Directory 1959. Two parts. (Pp. 2,980+lxiv. 84s.) London: J. and A. Churchill Ltd. 1959.

Nobody Need be Fat. By Robert Kemp, T.D., M.D., M.R.C.P. (Pp. 150+v. 12s. 6d.) London: William Heinemann, Medical Books, Ltd. 1959.

The Life of Sir Alexander Fleming, Discoverer of Penicillin. By André Maurois. Translated from the French by Gerard Hopkins, and with an introduction by Professor Robert Cruickshank. (Pp. 293; illustrated. 25s.) London: Jonathan Cape. 1959.

British Obstetric and Gynaecological Practice. Edited by Sir Eardley Holland, M.D.(Lond.), F.R.C.P., F.R.C.S., F.R.C.O.G., and Aleck Bourne, M.A., M.B., B.Ch.(Cantab.), F.R.C.S., F.R.C.O.G. Obstetrics by Sir Eardley Holland. Second edition. (Pp. 1,228+xiv; illustrated. £7 7s.) London: William Heinemann, Medical Books, Ltd. 1959.

Glaucoma. Transactions of the Third Conference, January 8, 9, and 10, 1958, Princeton, N.J. Edited by Frank W. Newell, M.D. (Pp. 272; illustrated. $5.25.) New York: Josiah Macy, Jr. Foundation. 1959.

Protides of the Biological Fluids. Proceedings of the Sixth Colloquium, Bruges, 1958. Edited by H. Peeters. (Pp. 330+ix; illustrated. 45s.) Amsterdam, London, New York: Elsevier Publishing Company. 1959.

Atomic Medicine. Edited by Charles F. Behrens, M.D. Third edition. (Pp. 705+xiv; illustrated. £6.) London: Baillière, Tindall and Cox, Ltd. 1959.

Reproduction and Infertility. III Symposium, Colorado State University, Fort Collins, Colorado. Edited by F. X. Gassner; Associate Editors, Rue Jensen, H. J. Hill. (Pp. 273+vi; illustrated. 42s.) London, New York, Paris, Los Angeles: Pergamon Press. 1958.

Le Sommeil de l'Enfant avant Trois Ans. By Robert Debré and Alice Doumic. (Pp. 195+xii; illustrated. 800 Fr.) Paris: Presses Universitaires de France. 1959.

The Nature of Stress Disorder. Conference of the Society for Psychosomatic Research held at the Royal College of Physicians, May 1958. (Pp. 298; illustrated. 25s.) London: Hutchinson Medical Publications. 1959.

Ciba Foundation Symposium on Carcinogenesis. Mechanisms of Action. Editors: G. E. W. Wolstenholme, O.B.E., M.A., M.B., B.Ch., and Maeve O'Connor, B.A. (Pp. 336+xii; illustrated. 48s.) London: J. and A. Churchill. 1959.

Cancer of the Skin. By John C. Belisario, C.B.E., E.D., M.D., Ch.M., D.D.M. (Pp. 321+xvii; illustrated. 50s.) London: Butterworth and Co. (Publishers) Ltd. 1959.

The Effect of Advancing Age upon the Human Spinal Cord. By L. Raymond Morrison, M.D., with the collaboration of Stanley Cobb, M.D., and Walter Bauer, M.D. (Pp. 127+x; illustrated. 48s.) Cambridge, Mass.: Harvard University Press. London: Oxford University Press. 1959.

Report of the FAO Nutrition Meeting for Europe, Rome, Italy, 23-28 June, 1958. (Pp. 28+ix. 2s. 6d.) London: Her Majesty's Stationery Office. 1959.

Some Facts about Cerebral Palsy. (Pp. 20. 1s. 6d.) London: British Council for the Welfare of Spastics. 1959.

Ar oplastia. By A. Radulescu and N. Robanescu. (Pp. 174; illustrated. Lei 24.30.) Bucharest: Editura Academiei Republicii Populare Romîne. 1958.

International Textbook of Allergy. Edited by J. M. Jamar, M.D. (Pp. 639; illustrated. £5 10s.) Oxford: Blackwell Scientific Publications. 1959.

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MIST. N.H.S. CO.

In every country of the world where the patient can obtain drugs free of cost to himself the price that has to be paid is a source of constant worry to those answerable for insurance funds or government exchequers. The appetite grows with what it feeds upon. Modifications of the Australian idea of having a selected list of "life-saving" drugs on the free list seem on the whole to be more popular than the paternal British scheme of giving everyone everything apparently for nothing. In Britain the social security proposition that there should be no financial barrier to treatment has been interpreted as no direct payment at the time of illness or indisposition on the part of the patient. Both the Hinchliffe Committee (whose report, now published, is briefly summarized in this week's *Supplement*) and the recent Scottish Committee on Prescribing Costs[1] are opposed to any change in the British system. The Scottish Committee admits that "if a patient were prescribed only the drugs on the limited list he would not suffer medically"; but it fears the possibility that "in certain circumstances an impression might be created that the National Health Service offered only a utility service. . . ." It is frightened of an impression. The Hinchliffe Committee also comes down on what it describes as any limitation on the doctor's right to prescribe. With a neat piece of casuistry it suggests that a free drug supply is bound up with the clinical and academic freedom of the general practitioner. Nevertheless, in a section on prescription charges the committee states that "the object of the charges was not only to reduce the net cost to the Exchequer directly by the amount of the charges paid by patients, but also indirectly by discouraging demands on doctors—for example, for simple household remedies which patients might reasonably be expected to buy for themselves." Other countries seem to have been successful, and even highly successful, in satisfying both medical profession and public by ensuring that people who are ill should have freely the indispensable remedies for the illness, but that those who only need symptomatic treatment for temporary indispositions should pay for their "tonics," headache pills, and laxatives.

So long, therefore, as we continue to accept the position in this country that the public must not be asked to pay directly for minor remedies for minor maladies, then elaborate analyses of the cost of drugs are necessary, various kinds of restrictions have to be considered, and admonitory statements have to be issued. The Scottish Committee in particular, stressing "the sense of financial responsibility of the doctors who prescribe," recommend that there should be courses of instruction for senior students and junior medical staff on the cost of prescribing, a recommendation that was made by the recent report of the Select Committee on Estimates. The Hinchliffe Committee, however, comes to the welcome conclusion that "it is not expedient to make statutory provision for a compulsory examination in costs as part of the medical curriculum. . . ." The fact that these two committees have thought it necessary to make these observations suggests that there is something radically wrong either with medical education or with the way the pharmaceutical services are administered under the National Health Service Acts. The crux of the matter is put in a statement from a medical school to the Hinchliffe Committee: "We believe that the duty of the teaching school and hospital is to teach students the principles of sound therapeutics and prescribing, and to teach newly qualified doctors to put them into practice in their pre-registration year. We believe that good prescribing is generally economical and that teaching about cost ought to take second place, but we do point out that certain drugs are costly, and we also recommend that the *National Formulary* should be used unless there are strong reasons to the contrary." We wish there had been still greater stress on sound education in therapeutics and pharmacology. The only real economy lies in good treatment. To try to turn medical students and newly qualified doctors into pricing clerks is absurd, especially in view of the Hinchliffe Committee's main conclusion that "there is no evidence of widespread and irresponsible extravagance in general practitioners' prescribing." The committee adds, however, that there is scope for economy and that some waste is involved in the present tendency to order larger

[1] *Brit. med. J., Suppl.*, 1959, **1**, 202.

quantities on each prescription. It suggests that posters might be displayed in doctors' surgeries warning patients "against getting the medicine habit." Would not general practitioners think that it is their job to tell their patients this? Another remedy advocated is the establishment of a prescribers' journal "independent of the pharmaceutical industry and of the Ministry of Health." But in the same breath the committee recommends that "the journal should be published and distributed by the Ministry of Health, who might also be asked to pay for the editorial organization." It would be difficult for a cost-conscious Ministry to be financially responsible for such a journal and allow it to be independent. There would seem to be much in this suggestion, but if such a periodical were to command the confidence of the profession, and in the eyes of the pharmaceutical industry be at least free from bias, then some publisher other than the Government should be sought. The committee makes an odd comment about delay in publication of the results of clinical trials—we wonder what the evidence for this is.

These are some criticisms to make of a report which nevertheless provides the profession and the public with an exhaustive and painstaking analysis of a highly complicated problem. Everyone will agree with the committee's conclusion that the main factors responsible for the drug bill are the coincidental introduction of a free and comprehensive N.H.S. and the discovery and large-scale production of valuable but expensive drugs. Other contributory factors are inflation, prescription charges, and changes in the population (more old people). The stress in both the Scottish and the Hinchliffe reports is, of course, on cost, because that is what they were asked to investigate. The keepers of the public purse will always be looking for ways and means of economizing on a free National Health Service which this country has decided to provide for itself. Unfortunately there is the inevitable tendency in anything that is nationalized to approach its problems in a negative, restrictive fashion. The Hinchliffe Committee admits that there are, to quote one of its headings, "compensating benefits from present expenditure on drugs." This is a characteristic English understatement. The committee records the fact that in 1948 regional hospital boards were "trying desperately to increase their accommodation for the tuberculous." It goes on to add that now "beds in many sanatoria are used for other purposes"—because of the great triumph of the new antituberculous remedies that have been introduced since the initiation of the N.H.S. Other matters the report refers to in this way are the effect of antibiotics on pneumonia, which before the war often involved expensive hospital treatment; of antibiotics on acute mastoid infection; and of tranquillizing drugs in shortening a patient's stay in a mental hospital. The committee could not, of course, estimate the cost of these and many other numerous benefits of the drug treatment of disease. But it is "concerned to note the totally inadequate publicity given to the remarkable saving in life, improvement in health, increase in efficiency, and saving on expensive institutional treatment which all stem from, among other things, the use of new drugs. We urge the Minister of Health to consider ways and means of publicizing these facts in a telling manner."

It is difficult, and perhaps impossible, to put on the opposite side of the balance sheet the crude financial benefit of all this, quite apart from the relief from suffering and pain, the prolongation of life, the increase of well-being and happiness. Bodies like the Select Committee on Estimates and Government officials seem so often to ignore these benefits, so obsessed are they with the cost of providing a health service at a time when medical science, and so practice, is expanding at a phenomenal rate. While doctors and medical schools will study carefully the recommendations of the Hinchliffe and the Scottish Committees, they will probably conclude that in the last analysis what really matters is sound undergraduate education in therapeutics and continued postgraduate reading and courses throughout a doctor's working life. Good prescribing is economical; but economical prescribing is not necessarily good.

TREATMENT OF HAEMATEMESIS AND MELAENA

In Great Britain one of the most frequent medical emergencies is haemorrhage from the stomach, the lower part of the oesophagus, or the duodenum. Mortality figures are difficult to compare because of the effect of age and of the site of the haemorrhage.[1] B. B. Crohn[2] has tabulated figures from some published series of cases treated conservatively and treated by surgery, and the overall mortality rate varied from 0 to about 25% after exclusion of those series with small total numbers. The average mortality for all series was about 10%. It would seem probable that E. Meulengracht's[3] introduction of early and liberal feeding had the effect of lowering the mortality rate, for he has published a series of 1,031 cases with a mortality rate of only 2.5%.[4] The

advent of the blood bank must also have had a beneficial effect, for it is now the usual practice to transfuse blood liberally, not only to save the patient from the results of the initial haemorrhage but to render him fitter to withstand a further haemorrhage, if it should occur, or to undergo emergency surgery, if this should prove necessary.

In spite of these therapeutic measures and in spite of the feasibility of operating in an emergency, it is difficult to prove beyond all doubt that present mortality figures are better than earlier ones. The variation is very great, and the beneficial effect of these therapeutic advances on the overall mortality rate has probably to some extent been hidden by the fact that many of the recent series seem to contain a higher proportion of old people. Two series published from Newcastle[5 6] give a good indication of the variation which can occur even in the same hospital. In the first, collected during the years 1941–8, there were 170 patients, of whom 16% were aged 60 or over, and the mortality rate was 2.4%; in the second, collected from 1949 to 1951, there were 358 patients, of whom 30% were aged 60 or over, and the overall mortality was 5.3%. N. C. Tanner[7] has also published a notable series of over 900 patients, with mortality of about 10%, but 40% of his patients were over the age of 60 years.

Are there any other ways by which we may reduce this mortality still further? The use of continuous or intermittent aspiration of the stomach in order to obtain early information of recurrent haemorrhage and to gain more precise diagnostic information[8] has been advocated. In some centres also emergency radiology is used to determine the site of the bleeding.[9] These two techniques might render the present methods of tackling the situation more precise and efficient, but beyond this they offer no new therapeutic approach. Some thirty years ago it was a frequent practice to apply ice-packs to the epigastrium, and recently workers in Minneapolis[10] have suggested that efficient local hypothermia might be effective. They have shown, by means of experiments on animals, that generalized hypothermia will retard considerably the digestive activity of the stomach, and they suggest, with some experimental support, that local hypothermia will produce a similar effect in man. They carry it out by perfusing an intragastric balloon with an alcohol–water mixture at a temperature of 2–5° C. This procedure resulted in a decrease in the volume of gastric juice secreted in a given time, though there was little change in the *p*H.

The authors do not discuss the effect of cooling on blood coagulation and how this might affect the bleeding areas. The point may be important, for R. G. MacFarlane[11] has shown that the clotting time depends very greatly on temperature, being shortest at 37° C. and greatly prolonged as the temperature falls below about 25° C. The surgeon would also have to consider how gastric cooling would affect operative mortality if an emergency operation had to be carried out in spite of the treatment.

The value of any new method does not in the end depend on theory but on carefully appraised results. Usually these can be obtained only by means of a properly designed and carefully executed clinical trial. Unfortunately the Minneapolis workers have given the case reports of only five patients treated by their method. Haemorrhage ceased in all, but so it does in the majority of patients not so treated, and it is impossible to decide from the evidence so far whether this is a sound form of treatment. Any clinical investigation of such therapeutic methods should preferably be carried out from the start in such a way that a definitive answer will emerge. This is no easy matter, for if the mortality of the controls were to be 7% (and if it turned out to be much higher one might question the efficiency of the orthodox therapy) about 400 patients would be needed in each group to show that even halving of the mortality was likely to be due to the new form of therapy.

[1] Jones, F. A., *Modern Trends in Gastro-Enterology*, 1952, Butterworth & Co., London.
[2] Crohn, B. B., *J. Amer. med. Ass.*, 1953, **151**, 625.
[3] Meulengracht, E., *Lancet*, 1935, **2**, 1220.
[4] —— *Arch. Intern. Med.*, 1947, **80**, 697.
[5] Ogilvie, A. G., and Spencer, I. O. B., *Brit. med. J.*, 1950, **2**, 138.
[6] —— Cardoe, N., and Bentley, F. H., ibid., 1952, **2**, 304.
[7] Tanner, N. C., *Edinb. med. J.*, 1951, **58**, 293.
[8] Chandler, G. N., and Watkinson, G., *Quart. J. Med.*, 1958, **27**, 564.
[9] Schatzki, S. C., and Blade, W. R., *New Engl. J. Med.*, 1958, **259**, 910.
[10] Wangensteen, O. H., Root, H. D., Jenson, C. B., Imamoglu, K., and Salmon, P. A., *Surgery*, 1958, **44**, 265.
[11] MacFarlane, R. G., *J. clin. Path.*, 1948, **1**, 126.

ADVICE ON RADIOLOGICAL PROTECTION

So many official reports on radiation hazards have appeared in recent years that anyone may be excused for wondering what place should be accorded to the latest recommendations of the International Commission on Radiological Protection, which have just been published.[1] There have been reports from the Medical Research Council and from the United States National Research Council, from a special committee set up by the United Nations to study fall-out hazards and another set up by the United States Senate for the same purpose, while the Adrian Committee in Great Britain

[1] *Recommendations of the International Commission on Radiological Protection*, 1958, London.
[2] *Radiological Hazards to Patients*. Interim report of the Committee, 1959. H.M.S.O., London. 1s. 3d. net.
[3] *Brit. med. J.*, 1959, **1**, 1232.

continues its study of the population dose due to medical radiology and recently issued an interim report.[2 3]

It would be invidious to claim that the I.C.R.P. is any more "official" than some of these other bodies, especially as the relatively small group of internationally known experts in the subject have served, in different combinations, on all these committees or have at least provided the evidence. Each of these special committees has had a particular task to do, and has, as a rule, ceased to exist after issuing its report. The task has often been to determine whether the maximum permissible levels of radiation have been reached or might be reached in given circumstances. The I.C.R.P., on the other hand, has had the subject of radiological protection continuously under review since 1928, when it was set up as a permanent body by the International Congress of Radiology, to which it reports every three years. Its task has been the more general one of determining what levels of radiation shall be considered permissible. It consists not of a number of national delegations, but of independent scientists from many countries, each of whom has been appointed because of his international reputation in the field. It is thus able to speak with independence and authority.

In its early years radiation was an occupational hazard affecting a relatively small number of people; to-day it is a matter which concerns the whole population. The I.C.R.P. has moved with the times while still preserving its traditional caution and thoroughness. These latest recommendations from the main Commission deal not only with the permissible occupational exposure but also with levels of permissible exposure for the whole population and for special sections of it. The experimental and observational data on which they are based will be presented in greater detail in the reports which are still to be published from the Commission's five special committees.

It is remarkable that the I.C.R.P. has done this work for more than 30 years with no permanent secretariat and practically no funds, drawing heavily on the voluntary services of the experts who form its committees and finding from various sources the small expenses necessary for their occasional meetings. Whether it can continue indefinitely along these lines would seem to be doubtful, but if extra funds or facilities are needed to enable it to discharge its greatly increased tasks and responsibilities it is to be hoped that they will be provided without prejudicing in any way the independent scientific status of the Commission.

BREAST ABSCESS

One of the arguments in favour of domiciliary confinement is that infections, both maternal and neonatal, occur less often in the home than in the hospital. In a paper on breast abscess in last week's *Journal* (p. 1224) Mr. I. C. S. Knight and Mr. B. Nolan report that they found in Edinburgh that the incidence of breast infections in 1957 was more than twice as high in women delivered in hospital as in those confined at home. They studied 100 consecutive cases of puerperal breast abscess requiring surgical treatment. The causal organism was *Staph. aureus* in every case. The infections were associated with heavy colonization of the baby's nasopharynx with organisms of the same type as those cultured from the abscess but differing from those carried in the mother's nares. Indeed, 46 of the babies showed some infective lesion, most commonly of the skin. In over 90% of the cases the causative organism was insensitive to penicillin. This is not surprising. In most hospital maternity units this has been so apparent clinically for some years now that penicillin is not used for breast infections as the antibiotic of first choice pending the results of sensitivity tests. In the Edinburgh series chloramphenicol was found the most effective antibiotic: resistance to it occurred in one case only. But this was in 1957, and it would be interesting to learn what increase in rate of resistance to this drug has developed since then. Knight and Nolan recommend that when infection is suspected an antibiotic should be given, but discontinued if there is no clinical response in 48 hours.

The Edinburgh workers found that breast abscess appears to be a more protracted disease than in pre-antibiotic days. Abscesses healed more quickly when lactation had failed than when it had been suppressed, and further abscesses seemed much more likely to occur when lactation had not been completely suppressed. The woman urged to "breast-feed" while in hospital, but giving up as soon as she returned home, was more prone to infection, presumably because in her case the measures taken to dry up the breasts were inadequate. This raises the question whether hospital staffs, perhaps largely for their own convenience, too often insist on a mother breast-feeding while in hospital, even though it is obvious she will desist as soon as she returns home. There is another more important question which might be asked: If the hospital is the safest place for labour, but home the safest after delivery, is there not a strong case for the very early discharge from hospital of mothers and infants after a normal confinement?

NOMENCLATURE OF BLOOD-CLOTTING FACTORS

The possibility of international agreement on the nomenclature of blood coagulation factors has always seemed as unlikely as major agreements in international politics. Five years ago a number of leading workers decided that an international committee should be formed as a preliminary step to attempting to propose a standardized nomenclature for the factors which are generally believed to play a part in the physiological clotting of blood.[1] That an important measure of agreement has now been reached by this committee under the chairmanship of Dr. Irving S. Wright is a

[1] See annotation, *Brit. med. J.*, 1957, 1, 278.

great achievement which may mark the beginning of a more rational approach to the whole subject. The fact that the committee has members from all parts of the world, some of whom have strong and independent views on nomenclature, is evidence of the skill of the chairman, under whose guidance good sense and friendship have triumphed over pride and prejudice.

To experts in the field of blood coagulation the achievement may seem disappointingly modest. The committee has agreed to accept the evidence for the existence of four coagulation factors in addition to prothrombin, fibrinogen, tissue extracts, and calcium. These four factors are defined with the synonyms in common use, and an international nomenclature in roman numerals has been proposed—factors V, VII, VIII, and IX. The definitions of these factors can be found in an article recording the committee's decisions at p. 1292 in this issue.

In addition to defining and accepting these factors the committee has laid down the evidence which will be required for the acceptance of new factors in the future. This part of the document is of great importance and should act as a guide to workers in the planning and description of their researches. A clinical haemorrhagic syndrome associated with deficient coagulation in which the defect is corrected by normal and defined pathological specimens of plasma or blood does not constitute evidence for a new factor. Methods for the assay of the physiological properties of the factor must also be presented.

Acceptance of a factor by the international committee does not necessarily confer any high order of reality on it. The acceptance means that the committee is reasonably satisfied that the phenomena on which the proposed factor is based are sufficiently clear cut and reproducible for description. In the future a factor previously accepted by the committee may be deleted if new evidence requires this. The committee is rightly interested mainly in clarity in the communication of ideas.

The statement describing the results of the committee's deliberations, published simultaneously in England and America, should form the basis of future action in many spheres. For example, editors should try to ensure that, for factors accepted by the committee, the international nomenclature should be used in their journals—at least in brackets after the locally accepted term—and that unauthorized extensions of the roman numerical system do not appear in print. Workers who make a new discovery will now have the requirements for the acceptance of a factor clearly before them and may be encouraged to resist the temptation to add to the nomenclature before they are sure that they have adequate evidence. The committee will itself in due course be required to come to some decision about existing controversial syndromes. For example, no international nomenclature has been proposed for such syndromes as the Hageman defect, the Stuart-Prower defect, or plasma thromboplastin antecedent deficiency. Faced with these problems the committee will be greatly helped by its own admirable and clear criteria.

IDIOPATHIC RENAL ACIDOSIS IN INFANCY

In the years following the second world war renal acidosis became more widely recognized as a cause of the failure of some infants to thrive, but since 1953 it has become much rarer.[1] The symptoms of anorexia, vomiting, and constipation, with signs of dehydration, hypotonia, and low-grade pyrexia, are common to other diseases of this age group. The diagnosis depends on the finding of a urinary *p*H on the alkaline side of 6.5 in the face of an acidosis in the blood. Early diagnosis and treatment with alkalis result in the relief of symptoms and, after a period of time ranging from a few weeks to many months, in apparent cure.

Since the recognition of the syndrome of nephrocalcinosis by R. Lightwood[2] and its relationship to persistent acidosis,[3] the defect has been traced to an inability of the renal tubules to reabsorb bicarbonate,[4 5] probably because of defective action of the enzyme carbonic anhydrase.[6] Efforts to elucidate the aetiology further have been unsuccessful; they have had to take into account the peak incidence in Britain between 1948 and 1953, the possible relationship to idiopathic hypercalcaemia of infants,[7] and the self-limiting nature of the disorder. All this points to an environmental hazard, and, since breast-fed infants are rarely affected, a relationship to feeding seems likely. In the search for noxious agents overdosage with vitamin D and mercury ingestion have been considered, with inconclusive results[8 9]; failure to prove guilt, however, is by no means the same as saying that innocence has been established. When it is remembered that both mercury and vitamin D influence renal tubular function, the decline in incidence since vitamin-D supplements were reduced in infant foods and mercury removed from teething powders seems to be more than a mere coincidence. The difficulty in attributing the guilt to these substances, however, lies in the fact that only a few cases of renal acidosis have been reported with a high serum calcium, and a similar small proportion of infants with hypercalcaemia show an acidosis; in the case of pink disease, for which mercury has been blamed beyond reasonable doubt, acidosis is not a feature.

The self-limiting nature of renal acidosis in infants has been assumed from follow-up of individual cases. Recently E. U. Buchanan and G. M. Komrower[10] for the first time have produced convincing supporting evidence in an elegant study of renal function in eight children who had suffered from renal acidosis four or more years previously. They were found on physical examination to be essentially normal: their renal function was then compared with that of twenty-two

[1] Stapleton, T., in *Modern Trends in Paediatrics*, 2nd series, 1958, London.
[2] Lightwood, R., *Arch. Dis. Childh.*, 1935, **10**, 205.
[3] Butler, A. M., Wilson, J. L., and Farber, S., *J. Pediatrics*, 1936, **8**, 489.
[4] Hartmann, A. F., *Ann. Intern. Med.*, 1939, **13**, 940.
[5] Stapleton, T., *Lancet*, 1949, **1**, 683.
[6] Smith, L. H., and Schreiner, G. E., *J. Lab. clin. Med.*, 1954, **43**, 347.
[7] Lightwood, R., *Arch. Dis. Childh.*, 1952, **27**, 302.
[8] —— Payne, W. W., and Black, J. A., *Pediatrics*, 1953, **12**, 628.
[9] Carré, I. J., Wood, B. S. B., and Smallwood, W. C., *Arch. Dis. Childh.*, 1954, **29**, 326.
[10] Buchanan, E. U., and Komrower, G. M., ibid., 1958, **33**, 532.
[11] Kunz, H. W., Cheung, M. W., and Pratt, E. L., *J. Pediat.*, 1958, **52**, 434.

normal controls of similar ages by means of a carefully contrived routine of withholding and then forcing fluids, together with the administration of ammonium chloride. Results showed complete recovery of the ability to secrete an acid urine and to form ammonia. The authors conclude that infantile renal acidosis is a different condition from that associated with nephrocalcinosis in older children and adults and that the one does not lead on to the other. This is at variance with earlier views and does not exclude the possibility that milder cases escaping diagnosis in infancy may not present in later childhood with irreparable renal damage.[11] Further follow-up studies are obviously needed on both treated and untreated cases in order to determine this point.

IN THE MARKET PLACE

The manufacturers of drugs are often criticized for the methods they use to sell them. From time to time we publish letters complaining about the circulars which pour unceasingly through doctors' letter-boxes or about the time taken up in interviewing representatives. In their less irritable moments most general practitioners would agree that circulars can often be highly informative, and representatives sources of useful knowledge. Unfortunately the promotional efforts of the whole pharmaceutical industry tend to be judged in the light of the actions of the firms with the lowest standards. The Association of British Pharmaceutical Industry is conscious of the need for a high standard among its members, and, as its president, Dr. Thomas Kerfoot, mentioned in a speech the other day, a marketing code for "medical specialties" has been drawn up and accepted by every member of the association. Medical specialties are defined as "branded products not advertised to the lay public," and the two guiding principles to be adopted in promoting their sales are: (*a*) "that the accuracy and completeness of the information are of paramount importance, and (*b*) that the methods of promotion employed must be appropriate to the learning and professional status of those to whom they are directed."

The code lays down in general terms what should and should not be done. For instance, promotional activities should give a complete and balanced picture of the product to the doctor; side-effects and contraindications must be clearly stated; and statements based on clinical and pharmacological evidence must be clearly differentiated from those based on theoretical speculation. On the negative side, the code lays down that promotional activities must not mislead, that results which have been superseded by later work must not be used without qualification, and that disparaging references to competing products must be avoided. On the subject of "mailings," the code asks for sensible restraint in the frequency with which mailings on individual products are sent out, and communications must not be designed to gain attention by subterfuge or deception. The "basic N.H.S. cost" of products must be given in or with all promotional literature. The code also gives guidance on the work of representatives, on the distribution of samples, and on gifts and hospitality: gifts to doctors and pharmacists should be "of little monetary value" and hospitality and entertainment "must be moderate." The pharmaceutical industry has everything to gain by accepting in full this quite sensible code. Firms who contravene it may be excluded from membership of the Association of British Pharmaceutical Industry.

NEW DRUGS IN PSYCHIATRY

A technical report[1] has recently been published of a conference held by ten specialists and three members of the World Health Organization Secretariat to consider the subject of ataractic (or tranquillizing) and hallucinogenic drugs. The report is intended to help in their classification. Drawing attention to the few known facts and also to the many investigations needed into the mode of action of the drugs, the report suggests concerted international efforts at collecting statistically valid clinical observations from communities with as varied a cultural background as possible. It also summarizes recent progress in neurology, referring to electron-microscopy, electrophysiological studies with microelectrodes and micro-injection techniques, and microchemistry and histochemistry of the nervous system.

Changes produced in certain parts of the brain, such as the limbic system, the hypothalamus, and the reticular formation, may be related to the clinical effects produced by the ataractic drugs; the changes may include interaction of the drugs with some of the known chemical components of brain tissue, among them amines and amino-acids. However, this aspect is at present, though fascinating, also highly speculative, and apt to be modified with every new discovery. The ataractic drugs and hallucinogens should be of help in the classification of mental diseases, though progress on those lines has so far been meagre. Differences in action of psychotropic drugs in different cultural societies suggest further studies of the sociological aspect of psychiatry.

The report contains a most valuable—if only provisional—attempt at a classification of the ataractic drugs, based on a large number of experimental data collected from the literature. The authors point to the weakest point in our knowledge of these agents, which is the absence of good comparative data. Papers describing an effect produced by drug A usually make no attempt at comparing A with other drugs which might have the same effect, particularly with older remedies long known in therapeutics. It is important to realize that each individual drug has a characteristic pattern of action, usually not even shared by its nearest chemical congener. Workers actively engaged in research on neuropharmacology will greatly appreciate the long list of references and five pages of structural formulae of the agents discussed.

[1] *Wld Hlth Org. techn. Rep. Ser.*, 1958, 152.

Drug Treatment of Disease

TREATMENT OF DIABETES MELLITUS

1. INSULIN: PHYSIOLOGICAL AND THERAPEUTIC ACTIONS

BY

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It is about 35 years since Banting and Best discovered insulin, and, in spite of a vast amount of research, the exact mode of action of this hormone is still unknown. The structure of the insulin molecule has been brilliantly demonstrated by Sanger and his colleagues (Ryle *et al.*, 1955), who showed that insulin is a protein with a molecular weight of 6,000 or multiples thereof. Each molecule consists of two polypeptide chains held together by –S–S– linkages derived from the amino-acid cystine. The A chain is made up of 21 amino-acid residues and the B chain of 30.

It is convenient to consider first the actions of insulin and then the effects of such actions, as the former are more speculative than the latter and less directly related to its therapeutic applications.

Actions of Insulin

There are at least three sites at which insulin may act to facilitate carbohydrate metabolism.

1. Action of Insulin on the Transfer of Glucose into Cells

According to Levine and Goldstein (1955) and many others the most important single action of insulin in carbohydrate metabolism is to facilitate the transport of glucose across cell membranes. There is much experimental evidence in support of the view that this process is not one of simple diffusion but is an enzyme-catalysed or "carrier" transport process upon the rate of which depends the extent of glucose utilization. Factors other than insulin, such as anaerobiosis and certain chemical substances, are also known to affect the transport of sugars into cells (Manchester *et al.*, 1958). It has been suggested that, in the absence of insulin, the transport system is shielded in some way and that insulin and other agents may act by removing this shield.

2. Action of Insulin on the Phosphorylation of Glucose

Insulin may facilitate the phosphorylation of glucose within the cell. The work of Price *et al.* (1945) and others suggests that insulin acts with hexokinase in the conversion of glucose into glucose-6-phosphate, and that it neutralizes the inhibitory action on this system of growth and adrenocortical hormones. The validity of this hypothesis remains unsettled, but many now believe that the intracellular systems are controlled by factors other than insulin.

3. Action of Insulin on Transformations in the Citric Acid Cycle

This possible site of action was suggested by Krebs and Eggleston (1938). Quite apart from whether it is the entry into the citric acid cycle or the transformations within it that are impeded by lack of insulin, the net effect is defective production of adenosine triphosphate and consequent impairment of oxidative phosphorylation. Although it is not yet possible to say with certainty how or where insulin exerts its action, it is possible to be more definite about the effects of such action or actions; even so it may be difficult to decide whether they are directly or indirectly produced.

Effects of Insulin Action

Many effects are attributable to the action of insulin, but five only will be considered as being of particular importance in relation to the therapeutic action of insulin:

1. Increased formation of glycogen in liver and muscle.
2. Increased peripheral utilization of glucose.
3. Inhibition of gluconeogenesis and ketogenesis.
4. Increased synthesis of fat.
5. Increased synthesis of protein.

1. Opinions differ on whether the observed increase in liver glycogen produced by insulin is due to a direct effect of the hormone on the liver or entirely accounted for by the increased formation of lactic acid which results from its peripheral action.

2. The effect on the peripheral utilization of glucose can readily be demonstrated by estimation of the difference in blood-sugar level of arterial and venous blood after an injection of insulin (the A–V difference). Conversely, in diabetes utilization of glucose is impaired, and it was at one time thought that this accounted for the hyperglycaemia characteristic of the disease—the so-called "under-utilization" concept.

3. Prolonged starvation in man and animals produces a relatively small decrease in fasting blood-sugar level. If, however, an animal is adrenalectomized and then fasted, fatal hypoglycaemia is produced (Long, 1952). The same phenomenon is familiar clinically in severe Addison's disease; this tendency to hypoglycaemia is readily corrected by cortisone. The maintenance of the fasting blood-sugar level is therefore dependent on adrenocortical activity, which stimulates gluconeogenesis. This excessive production of glucose from protein and glycerol is a feature of severe diabetes, and accounts not only for the failure of carbohydrate starvation to correct the hyperglycaemia, but also for the characteristic negative nitrogen balance; it also gave rise to the "over-production" concept of the causation of the hyperglycaemia. "Under-utilization" and "over-production" are no longer rival theories, but are now together recognized as the immediate causes of hyperglycaemia in diabetes mellitus.

The effect of insulin in inhibiting gluconeogenesis can be observed in the correction by insulin of the negative nitrogen balance of the severe untreated diabetic, and in the restoration of growth in previously untreated or inadequately treated diabetic children; the latter is due also to the protein anabolic effect of insulin action referred to below.

In the absence of insulin action glycolysis is greatly reduced, and the availability of oxaloacetate decreased. In these circumstances the body can no longer derive the necessary energy directly from carbohydrate sources

and so turns to fat. Fatty acids are mobilized in excess of the katabolic capacity of the tissues, and the acetyl co-enzyme A which accumulates is converted into ketone bodies. It has recently been shown that fatty acids released from adipose tissue may be utilized directly by a number of tissues without prior conversion to acetoacetate or beta-hydroxybutyrate by the liver. The effect of insulin action in facilitating glycolysis restores the normal pathway of energy production and leads to the rapid disappearance of ketone bodies from the blood and urine.

4. It is now known that adipose tissue is normally capable of converting glucose to fatty acids and is probably the major site of this conversion. Experiments on rats with alloxan-induced diabetes have shown that insulin has a direct effect on the formation of fat from glucose. This is in line with the clinical observation that insulin therapy is often associated with an increase in body fat which may be so great that an undesirable degree of obesity results.

5. The anabolic effect of insulin action has been studied by Young (1937), Best *et al.* (1954), and many others, and there is now considerable evidence that insulin plays an important role in the process of protein anabolism and growth. Young showed that in the early stages of the production of experimental diabetes by anterior pituitary extract there is a phase of nitrogen retention and, in puppies, of excessive growth. This continues until hyperglycaemia develops and the animal becomes diabetic, when the nitrogen balance is reversed. It seems probable that the failure in insulin production is the result of exhaustion of the beta cells of the islets of Langerhans from overstimulation by growth hormone, and that nitrogen retention and growth continue only so long as the pancreas is capable of producing enough insulin. The response to adequate insulin therapy of the untreated diabetic child and often poorly controlled diabetic dwarf lends clinical support to an increasing volume of experimental evidence for this anabolic effect of insulin action.

Sulphonamide Hypoglycaemic Agents and Insulin*

In 1942, while investigating the chemotherapeutic action of the sulphonamide preparation I.P.T.D., Jambon *et al.* (1942) observed that it caused severe hypoglycaemia. The mechanism of this action was investigated by Loubatières (1955), but no attempt was made to apply it to the treatment of diabetes until 1955, when Franke and Fuchs (1955) recognized the hypoglycaemic action of the related compound N-(*p*-aminobenzene sulphonyl)-N_2-butylurea or carbutamide. Owing to the occurrence of toxic side-actions in a small number of diabetics treated with this drug its use has been abandoned in favour of tolbutamide, a chemically similar preparation with a CH_3 group in the *para* position in place of the NH_2 group of carbutamide.

The mode of action of tolbutamide, like that of insulin, is not fully understood; while both lower the blood sugar, it is not certain that they do so in the same way. Of the many theories put forward and possibilities investigated only three will be considered here:

1. Inhibition of Some Contra-insulin Substance or Substances.—Insulinase, glucagon, and adrenal and pituitary hormones all qualify for inclusion on the grounds that they destroy or are otherwise antagonistic to insulin, but there is no convincing experimental evidence that their action is inhibited by tolbutamide.

2. Increase in the Peripheral Utilization of Glucose.—Although it might appear relatively easy to determine whether or not tolbutamide has this action, this has not proved to be the case, but the majority of reports to date do not support this hypothesis.

3. Enhancement of the Action of Endogenous Insulin.—This last view receives strong support from the generally accepted fact that, when all endogenous insulin is absent, either as a result of pancreatectomy or treatment with alloxan, tolbutamide exerts no hypoglycaemic action. Clinically the same is true in the severe forms of diabetes most often seen in young or relatively young patients characterized by ketosis and a low plasma insulin. If, however, tolbutamide acts by stimulating the beta cells of the islets of Langerhans and so increasing the amount of insulin reaching the liver via the portal vein, it is difficult to explain why it reduces the output of glucose from the liver while exogenous insulin has no such action. This discrepancy might possibly be accounted for by a difference between the actions of exogenous and endogenous insulin.

The therapeutic importance of these observations is that a good response to tolbutamide is only to be expected in those relatively mild diabetics who do not tend to pass ketone bodies in their urine, and whose daily requirement of insulin, if any, does not exceed about 30 units; such cases are often middle-aged or old and not infrequently obese.

*A separate article, to appear shortly, will be devoted to sulphonamide derivatives and other hypoglycaemic agents.

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NOMENCLATURE OF BLOOD-CLOTTING FACTORS*

ACCEPTANCE BY THE INTERNATIONAL COMMITTEE ON NOMENCLATURE OF FOUR FACTORS, THEIR CHARACTERIZATION AND INTERNATIONAL NUMBER

Physicians often accuse basic scientists, chemists, and physicists in particular, of using a strange language which no one outside his own subject can understand, but at least the majority of physicists or chemists can understand what others in their own field are talking about. The field of blood coagulation is one in which medical men and biological scientists have created such chaos that they do not even understand what other workers in the field are talking about, far less the clinician or the medical student.

To improve international communications is a worthy object at any time: to do so in the field of clotting factors has proved a task of major difficulty. To bring together the prima donnas not only from different countries but from the same country, hold them together, and persuade them of the importance of a

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simple understandable classification has been the problem of the chairman of the International Committee. This activity, of course, has much wider significance than just the field of blood-clotting factors, and evidence for this wider significance has been the invitation by the National Advisory Heart Council of the United States to the members of this Committee to organize a series of international conferences within this field and to invite to these conferences young workers of exceptional promise so that they may listen to the discussion and benefit from the contact with their older colleagues from different countries in the world. The Committee therefore is making a major contribution to international communications in medicine, and it is hoped that this type of activity will be seen more frequently as the world grows smaller and nations more fully accept the necessity for living and working together.

The story of this Committee's work began at the first International Congress on Thrombosis and Embolism, held in Basel in 1954, when the multiple names for identical substances emphasized that the problem of international communication was a serious one in this field. The International Committee for the Standardization of the Nomenclature of Blood Clotting Factors was established. Twenty-two members from fifteen different countries were initially appointed. The list included the leading workers in the field, and most of the factors recently recognized had been discovered by them. The first meeting brought into the open the fact that they had to a considerable extent created the problem and they recognized that they had a moral and scientific responsibility towards unravelling it. It became clear that, though they had a paternal pride in the names of their choice, without their co-operation and compromise no progress could possibly be made. The efforts made by the members of the Committee to yield their own strong positions for the common good have been noteworthy.

One of the first decisions made by the Committee was that, whatever system of nomenclature was proposed, names should be avoided which implied an action by any factor. The reason for this had become clear when factors which previously had been given names implying function had later proved not to have that function but a different one. It was agreed that symbols should be used to designate blood coagulation factors until ultimately they were defined and identified in physical and chemical terms. However, certain essential physical and chemical data would have to be presented in support of the identity of any factor before the Committee would give it an international symbol.

With further study and negotiation over a three-year period, it became evident that only a numerical system fully met these qualifications, and, since some factors had already received roman numerals in addition to their names, it seemed logical to consider whether roman numerals would be suitable as the international symbolic code, allowing the author freedom to use whichever synonym he wished. Thus, one would write Factor V (proaccelerin) or Factor V (labile factor). The roman numeral would be intelligible in any language, including the Oriental. The first four factors are widely known by their names and some identified chemically, and roman numerals are perhaps less necessary. They are: Factor I—fibrinogen; Factor II—prothrombin; Factor III—thromboplastin (tissue); Factor IV—calcium. It seems likely that these names will continue in common usage, and in fact very few other names have been used for these factors.

One of the great problems facing the Committee was to decide when sufficient evidence was available to justify any factor or activity being assigned a number. It has been agreed as follows:

1. The minimal requirements for characterization of a clotting factor in whole blood, plasma, or serum shall be valid data on the reproducible effect on storage, adsorbability, inactivation by heating, effect of *p*H.

Additional chemical data are considered highly desirable if available.

2. A clinically identifiable state associated with an abnormality in the clotting mechanism shall be regarded as supporting the evidence for the lack or excess of a factor.

3. Methods of assay of physiological properties shall be listed. An appropriate selection of these methods will be considered as minimal for presentation of a factor before the Criterion Committee. In the case of previously undescribed factors the mechanism used for identification shall be clearly described by the author for study and possible acceptance by the Committee.

The Committee proposes to publish in detail elsewhere the criteria on which they have based their recommendation that four further blood-coagulation factors should be recognized and assigned international symbols—namely, Factor V, Factor VII, Factor VIII, and Factor IX. The following is, however, a brief summary.

Factor V

Synonyms.—Factor V (Owren). Proaccelerin (Owren). Labile factor (Quick). Plasma ac-globulin (Ware and Seegers). Thrombogene (Nolf). Proprothrombinase (Owren). Prothrombokinase (Milstone). P.P.C.F. (plasmin prothrombins conversion factor) (Stefanini). Component A of prothrombin (Quick). Prothrombin accelerator (Fantl and Nance). Co-factor of thromboplastin (Honorato).

Deficiency of this factor results in a haemorrhagic diathesis which is probably inherited and has been described as a parahaemophilia or hypoproaccelerinaemia. The first case was recognized and described by Owren (1947) in a beautiful study carried on under the most adverse conditions due to the Nazi occupation of Norway, while Dr. Owren was at the same time an active member of the underground resistance. Several additional cases have since been described. This factor seems necessary for the formation of the prothrombin-converting substance in the blood and in tissue extracts. Other interesting properties are fully described in the literature (Fahey *et al.*, 1948; Stefanini, 1950; Soulier and Larrieu, 1953).

Factor VII

Synonyms.—Factor VII (Koller). Proconvertin (Owren). S.P.C.A.—Serum prothrombin conversion accelerator (deVries, Alexander). Stable factor (Stefanini). Cofactor V (Owren). Serozym (Bordet). Kappa factor (Sorbye and Dam). Prothrombinogen ? (Quick). Co-thromboplastin (Mann and Hurn). Serum accelerator (Jacox). Prothrombin conversion factor (Owren). Prothrombin converting factor (Jacox).

Factor VII plays a part in the production of at least three groups of abnormal states as follows: (1) A congenital deficiency may produce haemorrhagic phenomena with purpura and bleeding from the mucous membranes. Many such cases have been described. (2) Acquired deficiency may occur in liver

disease, in vitamin-K deficiency, in the immediate neonatal period, and following the administration of prothrombinopenic agents such as the coumarin derivatives used in anticoagulant therapy. (3) Excesses of Factor VII have been found in certain states associated with a high incidence of thrombo-embolism such as the third trimester of pregnancy. *The level of this substance in the blood is species specific.* Deficiency results in a quantitative prolongation of the one-stage prothrombin time test. Factor VII accelerates the conversion of prothrombin to thrombin in the presence of tissue thromboplastin, Factor V, and Ca^{++}. It does not accelerate the interaction of platelet Factor 3 and Factors VIII and IX. It cannot rectify retarded coagulation due to Factor V deficiency. It is not essential for thromboplastin generation in the coagulating blood. Other interesting properties are fully described in the literature (Owren, 1949; Owren and Bjerkelund, 1949; Conley *et al.*, 1949; Alexander *et al.*, 1950; Stefanini, 1953; Owen and McKenzie, 1954).

Factor VIII

Synonyms.—Factor VIII (Koller). Antihemophilic globulin (Patek and Taylor). Antihemophilic globulin A (Cramer). A.H.F.—antihemophilic factor (Brinkhous). P.T.F.—plasma thromboplastic factor (Ratnoff). Plasma thromboplastic factor A (Aggeler). T.P.C.—thromboplastic plasma component (Shinowara). Facteur antihémophilique A (Soulier). Thromboplastinogen (Quick). Prothrombokinase (Feissly). Platelet cofactor (Johnson). Plasmokinin (Laki). Thrombokatilysin (Lenggenhager).

Factor-VIII deficiency represents the classical haemophilia A, which is well known as the hereditary haemorrhagic disease that occurs almost exclusively in males, but which is female sex-linked. The degree of Factor-VIII deficiency varies from patient to patient. Haemorrhage occurs in any tissues following minor injuries and is frequently very serious. Factor VIII enters into the early stages of coagulation with Factor IX and Ca^{++} to produce an intermediate product which reacts with platelet Factor 3. The result of this reaction in the presence of Factor V is a very active agent in prothrombin conversion. It is essential in the formation of blood thromboplastin. A deficiency (1) prolongs the clotting-time; (2) diminishes the thromboplastin formed; and (3) diminishes the prothrombin conversion (Tocantins, 1955; Biggs and Macfarlane, 1957).

Factor IX

Synonyms.—Christmas factor (Biggs and Macfarlane). Factor IX (Koller). P.T.C.—plasma thromboplastic component (Aggeler). Antihemophilic globulin B (Cramer). Plasma thromboplastic factor B (Aggeler). Plasma factor X (Shulman). Facteur antihémophilique B (Soulier).

Factor-IX deficiency produces haemophilia B, or Christmas disease, named after the now famous patient of Biggs and Macfarlane. This is usually a severe haemorrhagic disorder resembling haemophilia A and inherited in the same way. Studies of this disorder led to the discovery of Factor IX. Factor IX, like Factor VIII, is essential for the formation of intrinsic blood thromboplastin. It probably enters into reactions leading to the formation of this thromboplastin, forming with Ca^{++} and Factor VIII an intermediate product which then reacts with platelet Factor 3 and Factor V. It influences primarily the amount of thromboplastin formed and not the rate of its generation (Aggeler *et al.*, 1952; Biggs *et al.*, 1952).

New Factors under Consideration

A number of additional plasma and serum factors have been described by various workers who believe they have established that they play a part in physiological clotting of blood. These factors are now under study by the Committee, and if the evidence indicates that the claims are valid they will be assigned a roman numeral.

The ultimate contribution of this Committee to medical understanding and education will depend on the willingness of educators, editors, and authors to adopt this system in their day-to-day efforts to create the medical thinking and literature of the future.

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TRANSPORT OF LIFE IN THE FROZEN OR DRIED STATE*

BY

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We received with keen appreciation the invitation to contribute a paper on space transport of life in the frozen state to the Space Medicine Symposium, but we accepted with diffidence. We felt we had some knowledge of the biological effects of freezing, but we hesitated to stick our neck out into space. We did what could be done in a few days by consuming a heavy meal of space literature, much of it written by distinguished members of the British Interplanetary Society. Even so, our contribution relates to biology rather than to medicine, and to the planet Earth rather than to space. Moreover, it deals only with the freezing and drying of living organisms. The justification for the inclusion of the dried state is, firstly, that suspended animation is achieved in nature by desiccation more often than by freezing, and, secondly, that the ultimate aim of all biologists engaged in the preservation of life at low temperatures is to graduate from freezing to freeze-drying, so that the material can be kept on the shelf rather than in the deep freeze. We should add that even in our own field we shall make statements to which there are numerous exceptions.

Hazards Awaiting Space Travellers

We have confined our recent literary researches to the solar system; we read that on the moon there is no atmosphere, little if any water, and wide and sudden swings of temperature; that on Venus an atmosphere of CO_2, lacking water vapour and oxygen, lies above thick clouds which may be dust, petroleum products, or something else; that on Mars the temperature is comparatively benign, but that there is little water, except when the ice caps melt, little or no oxygen, but a great deal of CO_2 in its tenuous atmosphere; that on Mercury the temperature difference between the shady and sunny sides may be as much as 650° C., though the twilight zone, where something analogous to night and day occurs because of the oscillation of the planet, might be more tolerable from the thermal point of view. We read that Jupiter, Saturn, Neptune, and other outer planets have bitterly cold atmospheres composed of methane, ammonia, and hydrogen. To these hazards which await space travellers on arrival at any of the other planets must be added the hazards of getting there. Among these may be mentioned cosmic rays, especially those trapped immediately above the earth's atmosphere, hard *x* rays given out by the sun, particularly at the time of sunspot activity, and intense ultra-violet irradiation. Extremes of temperature will also be encountered. This catalogue may well be considered formidable by the Earthly biologist, and the object of this paper is to see if there is any relevant information in our accumulated knowledge of the effects of freezing and drying on living organisms.

Properties of the Lower Organisms

Life, in the sense of matter showing growth, reproduction, and irritability, as we know it on Earth, depends essentially on a cycle involving water, oxygen, carbon dioxide, and fixed nitrogen, and a temperature at which their interaction is possible. In lower organisms the chain of events is often arrested temporarily by drying or cooling without permanent damage to the system. Moreover, many lower organisms and most plants produce spores or seeds which have a very low water content and a negligible respiration rate, and thus have a high resistance to cooling, drying, and lack of oxygen.

Two hundred and fifty years ago Leeuwenhoek found that the little animals which he had observed microscopically in drops of water from ponds and gutters survived complete desiccation. In the later eighteenth century Spallanzani found that a few of the similar animals in hay tea survived freezing at the lowest temperature which he could produce, which was about −20° C. More recently, Russian scientists were able to culture bacteria and protozoa from frozen soil which they obtained in Siberia when digging up carcasses of mammoths frozen at least 50,000 years ago in the Pleistocene Age. Becquerel found that algae and fragments of lichens, spores of bacteria and moulds, and also minute animals including Tardigrades and Rotifers, survived the combined effects of dehydration, high vacuum, and cooling to temperatures approaching absolute zero, −273° C. He calculated that organisms which would survive only one year at +10° C. could remain in suspended animation for billions of years under these conditions. Arrhenius thought that, in the dry state, living forms had already been wafted through outer space and that the earliest forms of life on our planet might have come from some distant star.

To return to Earth, there are well-authenticated examples of seeds of higher plants which have remained viable for hundreds or even thousands of years under highly adverse natural conditions. Professor Keilin, in a recent lecture, cited the case of a water-lily which had become extinct and was known only from the work of early Chinese artists. Then, in about 1932, seeds of this lily were found in a desiccated and encrusted state in the bed of a lake which, according to local records, had been dried up for a thousand years. Some of the seeds were sent to Kew Gardens, and a few, after being cleaned up with sulphuric acid, germinated and the once extinct lily bloomed again. For the sceptical, we should add that it has been possible to check the antiquity of the remaining lily seeds by radioactive carbon dating. On the other hand, according to Brimble, and contrary to popular belief, wheat grains found in the tomb of Tutankhamen were not viable.

Preservation by Freeze-drying

Modern techniques of freeze-drying will no doubt extend greatly the types of life that could be preserved for long periods in the dried state, though, from the point of view of the biologist, it is unfortunate that work on reviving organisms after prolonged periods of suspended animation has lately been concentrated on preserving pathogens. So far as the biologist is concerned, therefore, it is likely that lower animals as well as spores and seeds of plants could be landed in

*Delivered at a meeting of the British Interplanetary Society, September, 1958.

good condition on another planet, provided that the effects of irradiation and overheating could be avoided. In fact, it would be difficult or impossible to exclude them from space vehicles, particularly if higher animals were transported. Unless the most stringent precautions were taken they would inevitably go along as fellow travellers. Further, some of the photosynthesizing organisms which take in an excess of CO_2 and put out an excess of oxygen might even become established on Mars. The chances would be particularly good in the case of some of the xerophytic plants, especially the symbiotic lichens, which to some extent provide their own micro-climate. It has, in fact, been pointed out that the apparent vegetation on Mars, if similar to anything found on Earth, has possibly evolved along the lines of the lichens. The possibility of carrying out a colossal experiment in evolution by the colonization of Mars with a few selected species of lower organisms is particularly fascinating in this year of the Darwin Centenary.

The problem of establishing animals on other planets is very different. Lichen-like vegetation might supply the basic plant food, but, even on Mars, the scarcity of oxygen, and low atmospheric pressure, must mean that the establishment of Earthly animal life, especially in its more complex forms (for example, mammals), would require the provision of micro-climates in which oxygen tension, humidity, and probably also temperature were adjusted. If animal life, in the sense of self-propagating matter ultimately dependent on plant food, has evolved at all on the planets, it must have done so along lines unknown on Earth. This may well have happened. It is not impossible to imagine matter based on ammonia, methane, and silicon instead of on water, oxygen, and carbon, having the properties of growth, reproduction, and irritability, and therefore showing the classic criteria of life. At the temperatures prevailing, however, any life based on biochemical reactions will be pretty sluggish, particularly on the outer planets, and it is to be doubted if evolution can have proceeded far. But, fortunately, these problems are outside our scope.

A Biological Problem

The biological problem of transporting any of the higher forms of animal life to the planets is sufficiently formidable. Clearly, a state of suspended animation (anabiosis) in which food, water, and oxygen requirements were abolished, would be highly advantageous in transit, and here we can be guided by a rapidly expanding body of knowledge on the long-term preservation at low temperatures of animal organisms and of their essential germ cells. Alaskan and Siberian insects provide good examples of anabiosis induced in nature by cold and persisting for many months. There are now reports of moth larvae remaining viable after being frozen and stored in liquid air under experimental conditions. Again, intertidal molluscs, necessarily exposed to air temperatures at low tide, are in some regions frozen and thawed twice a day during the winter. These molluscs are remarkably tolerant of having a large part of their body water converted into ice and of the hypertonicity of the residual fluids which results therefrom.

The situation is very different with vertebrate animals. Even the cold-blooded ones, which can adjust their bodies to a wide range of temperatures above zero, do not tolerate extensive freezing. There is no evidence that vertebrates can survive the conversion of all their body water to ice under natural conditions. Stories of revival of fish and frogs found frozen solid in blocks of ice probably depend upon the lower freezing point of blood and tissue fluids, so that the animals could remain unfrozen though surrounded by ice and would survive until they died of oxygen lack.

The young or hibernating warm-blooded animal has something in common with the cold-blooded animal in that its body temperature can be reduced to a few degrees above 0° C. without damage. The hibernating bat can actually survive in the supercooled state at several degrees below zero provided that it does not freeze. In all these cases, however, heart beat and respiration still proceed slowly, so that the state is not one of suspended animation. There is no evidence that the cold-blooded vertebrate or the young or hibernating warm-blooded animal has any dispensation from the damage caused by conversion of body water to ice. In adult non-hibernating mammals the position is still more difficult because breathing and heart beats cease when the internal body temperature is reduced to a level somewhere between 25° and 15° C. When cooled below that range the mammal is in a dangerous state without respiration or circulation, and, until recently, death was, in fact, supposed to be inevitable. This is now known not to be so, and by special methods mice, rats, and dogs and monkeys have all been revived from deep body temperatures approaching 0° C. after cessation of breathing and heart beats for up to one hour. Recovery is usually complete and, remarkably, tests on resuscitated rats have shown no impairment of memory or learning ability following the severe anoxia. The dogs and monkeys have shown no change in reflexes or in behaviour.

Supercooling

In the case of the hamster, a potential hibernator, which can be handled more easily in the range of body temperatures above freezing-point, the experiment has been pushed further and body temperature taken below zero by immersion in a bath at $-5°$ C. In these circumstances one or other of two things happens: the animal may start to freeze, or it may supercool. In the freezing animal, body water begins to be converted to ice in the superficial tissues, in which case the deep body temperature drops only very slowly below the freezing-point of the blood, $-0.6°$ C. Such animals have been resuscitated undamaged after being below freezing-point for up to one hour, at which point some 50% of the body water had been converted to ice. During supercooling the body temperature is not maintained by the latent heat of crystallization of water, and falls rapidly to that of the surrounding bath. The supercooled state may be terminated by the sudden crystallization of ice throughout the tissue fluids, which results in a rapid rise of body temperature to freezing-point and is very dangerous to the animal. If spontaneous crystallization does not occur, supercooled animals can be revived in perfect condition.

Kalabukhov recently suggested that bats and other mammals might be supercooled to lower temperatures and so kept in a comparatively stable state. It may be that the first space explorers will have bats in the spaceship. It must be emphasized, however, that the partly frozen or slightly supercooled animal without heart beats and respiration is in a highly unstable condition because many of the physico-chemical processes of life are going on at a reduced rate and almost certainly at relative rates quite different from normal. Chaos therefore arises. The same applies with even greater force to bodies without heart beat or

respiration at temperatures between 0° C. and +15° C., in which biochemical disorder is running wild. Much lower temperatures will be required to arrest biochemical and physical changes and so obtain a stable state in which the animal can be preserved indefinitely. The biologist is thus not within sight of obtaining long-term suspended animation in warm-blooded animals, or any other vertebrate, but it would be a mistake to suppose that he never will succeed.

In man, body temperature is now commonly reduced to about +28° C. for surgical purposes, but at this temperature the heart is still beating slowly, and natural breathing can, if necessary, be supplemented by artificial respiration. And here we would like to protest against the use of the expression "deep freeze" to describe hypothermia induced for surgical purposes. The condition is not one of deep freeze, and the implication is sadly misleading. The techniques actually used in human patients are remarkable enough without exaggeration. We refer, for instance, to Melrose's method of elective cardiac arrest induced by injecting potassium ions into the coronary circulation of subjects in which a systemic circulation of oxygenated blood is maintained by an artificial heart-lung machine. Only recently, Niazi and Lewis reported that a patient had survived cooling to a deep body temperature of +9° C. without circulating her blood stream through a pump oxygenator. The heart was at a standstill for one hour. After re-warming, the patient recovered consciousness and survived 38 weeks thereafter without any apparent alteration in neurological or intellectual functions. Before treatment she had been in the terminal stages of inoperable pelvic carcinoma with abdominal and pulmonary metastases. She eventually died from spread of the original disease. Nine degrees above freezing-point is the lowest body temperature so far recorded from an adult human being who subsequently recovered. In the future, temporary cooling to this degree may prove of great value in medicine and surgery and become a routine practice.

Conclusion

Science fiction notwithstanding, the prospect of suspending animation for indefinite periods in man by freezing him is remote. When it becomes practicable, will it help the exploration of space? Possibly: to carry a proportion of the crew of a spaceship in a state of suspended animation would reduce oxygen and food requirements. But that is not all. A frozen body would presumably be partly or even wholly immune from the effects of violent acceleration or deceleration, provided that it was well supported to prevent breakage. Again, the effects of whole body irradiation are greatly reduced at low temperatures. The dose of whole body *x*-irradiation which is lethal to 50% of mice is about 500 r. When their body temperature is reduced to 0.5° C. and heart beat and respiration have ceased, the corresponding figure is about 1,800 r—a greater degree of protection than is afforded by any of the known protective substances. The effect is probably associated with the state of comparative anoxia of the cold animal, but that degree of anoxia could not otherwise be obtained without severe damage. How far the protective effect of cold at 0.5° C. will be intensified at lower temperatures is not known. This aspect of the subject is worth pursuing.

We must also bear in mind that suspended animation for space travellers would avoid the effects of old age,

(*Continued at foot of next column*)

(*Continued from preceding column*)

from which they might otherwise begin to suffer on the longer journeys, and dispose of what we understand is the very tricky problem of burial in space. Finally, we would like to say this: it is evident that the first problems of space travel lie with the physicist, the engineer and the medical physiologist. But, at a later stage, perhaps a not very much later stage, the biologist will play an important part, and he (or she) will have a fascinating time in doing so.

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To-day's Drugs

With the help of expert contributors we publish below notes on a selection of drugs in current use.

Palfium (M.C.P. Pure Drugs).—This is a new, very powerful analgesic, discovered in Belgium, which has received some publicity under the names "R.875" and "jetrium." It is a synthetic drug of a new chemical type; its formula is (+)-1-(β-methyl-γ-morpholino-αα-diphenylbutyryl)pyrrolidine and its official name is dextromoramide. Tablets containing 5 mg. of the base in the form of its bitartrate, and ampoules containing 5 and 10 mg., are supplied.

This drug is at least as potent as morphine, and equally dangerous in its liability to cause addiction. The recommended dose for relieving post-operative pain is 5 mg. every six hours. The manufacturers say that single doses of 20 mg. may be given, and up to 80 mg. or even more in 24 hours, for inoperable carcinoma. However, a high incidence of side-effects has been reported on a dosage of 10 mg. every six hours; these include giddiness, which was frequent, severe respiratory depression, nausea, sweating, and headache.

A report of toxic side-effects, with references to the literature, has recently appeared.[1]

N.H.S. basic price: 100 tabs. 5 mg., 19s.; 10 amps. 5 mg., 5s. 9½d.; 10 amps. 10 mg., 7s. 0½d.

REFERENCE

[1] Brisset, C., and Dereux, J. R., *Presse méd.*, 1959, **67**, 546.

Tympalgin Ear Drops (Silten).—These contain phenylmercuric nitrate 0.1 g., benzocaine 1.5 g., ephedrine 1 g., phenazone 5 g., chlorbutol 1 g., potassium hydroxyquinoline sulphate 0.1 g., propylene glycol to 100 ml. They are intended for the treatment of otitis media and otitis externa.

Of the seven ingredients, two, phenylmercuric nitrate and potassium hydroxyquinoline sulphate, have an inhibitory action on the growth of bacteria and fungi. Three ingredients, benzocaine, phenazone, and chlorbutol have an analgesic or sedative action on mucosal surfaces (chlorbutol is also a fungistatic), while ephedrine, by its decongestive action, facilitates drainage of exudate from the middle ear.

While it is logical to combine substances with an antibacterial, decongestive, and sedative action, the advantages of using no fewer than six ingredients (apart from the vehicle) are not obvious. Benzocaine and ephedrine do reduce pain and congestion in some cases. A point to bear in mind is that it is doubtful whether fungi are ever pathogenic in otitis media or externa; it is probable that they are present only as secondary and harmless contaminants. The topical application of cortisone derivatives is of special value in otitis externa.

N.H.S. basic price: ½ fl. oz., 2s. 7d.

Correspondence

Because of heavy pressure on our space, correspondents are asked to keep their letters short.

Circulating Anticoagulants

SIR,—The report of Dr. W. M. R. Henderson (*Journal*, March 21, p. 764) that cortisone and prednisolone apparently improved the clinical condition of his patient who had a circulating anticoagulant is of great importance, because such patients present a difficult therapeutic problem. Transfusions often accentuate the condition and increase the titre of the anticoagulant. A patient similar to the one of Dr. Henderson was studied repeatedly by my associates and me.[1] His titre of the anticoagulant (antithromboplastinogen) was so high that one part of his plasma inactivated the thromboplastinogen (factor VIII) in nine parts of normal plasma. He, too, had a haemorrhage into his larynx, and died from uncontrolled bleeding following a tracheotomy. Another patient who developed this disease had a spontaneous and permanent recovery after several months. It would be interesting to know whether cortisone would have shortened the course of her disease.

The development of antithromboplastinogenaemia in haemophilia is not uncommon, and apparently results from transfusions. It should be looked for whenever a patient fails to respond to fresh blood or plasma transfusions. A recent experience furnishes a good illustration. A boy aged 14 years who had severe haemophilia developed a large haematoma of his arm, then had haematuria, and soon thereafter had rectal bleeding. The loss of blood was so great that he required in one day 1,250 ml. of plasma and 1,000 ml. of blood. It was found that when he was given 250 ml. of fresh frozen plasma the clotting time increased from 30 to 36 minutes, the prothrombin consumption time remained unchanged at 8½ seconds, and the prothrombin consumption time with added aged serum and haemolysate increased only from 8½ to 11 seconds. This clearly indicated that he was inactivating the thromboplastinogen of the donor's blood, which accounted for his failure to respond to transfusions. On giving this boy cortisone, the rectal bleeding was controlled and he promptly recovered. When he was again studied five weeks later, a low titre of antithromboplastinogen was still present in the blood, although he was clinically well. It would seem advisable in such a case to give a drug of the cortisone group whenever he requires a transfusion.—I am, etc.,

ARMAND J. QUICK.

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Milwaukee, Wisconsin.

REFERENCE

1 Quick, A. J., Daniels, E. R., and Hussey, C. V., *J. Lab. clin. Med.*, 1954, **44**, 94.

Oral Antidiabetic Agents

SIR,—Since an earlier article on the use of oral antidiabetic compounds and the selection of suitable cases for such therapy[1] several new products have become available. The latest, from Germany, is "metahexamide," which is as effective as tolbutamide, but in much lower doses. It also has a longer duration of action which usually permits the control of suitable diabetics—elderly non-ketotic cases—with a single dose of up to 250 mg. administered each morning. We have now used this compound both by mouth and by injection for tests in twenty patients without serious side-effects, though therapy had to be discontinued in one case due to nausea and a transient papular rash.

It seems to us that these oral antidiabetic compounds will be prescribed with easier minds as more is known about their safety, their mode of action, and their effect on diabetic complications. As to the first point, about one million diabetics have been or are being treated with tolbutamide. Large-scale trials of metahexamide, of which our own is but a very small part, are being conducted by others in this country and abroad, to determine if this compound is equally safe.

We have been more concerned with the second point—their mode of action. The German hypothesis has been that these compounds stimulate the secretion of endogenous insulin from residual, functioning β-cells. One way to study this in man was to look into the glucose uptake by the forearm tissues. We find that there is a tissue glucose threshold in the periphery which must be exceeded in the blood in order to shift glucose into the tissues.[2] This threshold is elevated in diabetics and reverts towards normal after insulin and after successful control of diabetes by oral antidiabetic compounds[3]; in other words, the peripheral effects of insulin and of the oral compounds are apparently similar.

There are several possible explanations of these findings besides the hypothesis above. One is a direct effect of the oral compounds on the peripheral tissues; there have been reports of increased glucose uptake by the isolated rat diaphragm when tolbutamide or phenethyldiguanidine were added *in vitro*.[4,5] Another possibility would be the local augmentation of insulin action. However, neither of these alternatives has been substantiated by our studies with metahexamide, which appears to have the same general threshold-lowering effect as earlier compounds. Metahexamide, 1 mg./min., infused for 20–60 minutes into the brachial artery of three diabetics and two healthy control subjects, did not cause a statistically significant increase of local glucose uptake. Nor have we thus far observed any local augmentation of insulin effect; 0.1 unit of glucagon-free insulin intra-arterially alone caused a mean rise of glucose uptake of 148 mg./100 ml. forearm/min. over the ensuing 40 minutes in four subjects. When the same forearms were infused with metahexamide intra-arterially, 1 mg./min. before (20 minutes), during, and after (40 minutes) the same dose of insulin, the mean increase of uptake following the insulin was only 83 mg./100 ml. forearm/min.

All the foregoing evidence is admittedly indirect, but it has the merit that it was collected by observations in man. Nothing found so far contraverts the suggestion that the oral antidiabetics stimulate the secretion of endogenous insulin. Future work may confirm this as the correct explanation of their mode of action, and, perhaps more important, decide whether control of the blood sugar with such compounds arrests the course of diabetic complications.—We are, etc.,

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C. HARDWICK.

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5 Williams, R. H., Tyberghein, J. M., Hyde, P. M., and Nielsen, R. L., *Metabolism*, 1957, **6**, 311.

College of Pathologists

SIR,—Your leading article (*Journal*, May 2, p. 1171) on a College of Pathologists is of vast interest. I am too old to be much concerned, but during the last 25 years I have thought much about this and cognate matters, such as the relationship between universities and colleges, and have had many paradoxical and some amusing experiences.

Firstly, I wonder how many of us realize how our university medical schools have abdicated their authority on clinical affairs to outside institutions over which they have no control, so that now our university clinical departments are little more than subcommittees of various Royal Colleges. If any university should specify that applicants for (say) the chair of chemistry must be Fellows of the Royal Institute of Chemistry, and regard a university degree as not worth mentioning, there would be something of a rumpus. Yet this very strange condition applies so strictly in medical schools that we now have university professors and heads of departments who lack even a bachelor's gown—that is, until given one for reasons of sartorial or Senatorial propriety.

Secondly, I know a man who was not even short-listed for a consultant's appointment in pathology, until, on advice from a wise old colleague, he played down his M.R.C.P. diploma and played up a doctorate earned in pathology. He was a consultant in less than one year afterwards. This is one of the amusing things, but I realize that fundamentally it is quite reasonable.

Thirdly, granting your premise that pathology is *the* basic medical science, a year ago I had the amusing experience of reading a letter written to all the Faculty by a physician who had some grouse or other about the "ancillary service" of pathology. He is a tolerably learned physician, but clearly the basic education of specialists is no longer what once it was, for I am assured he meant no disrespect. Granting once again your premise, I begin to think that the pre-eminence of pathology in scientific medicine (and no other sort concerns us) is better manifested in the absence of a special college for it. Our present colleges appear to stream-off physicians, surgeons, and now gynaecologists into institutions which more and more threaten to isolate them.—I am, etc.,

Hospital for Women,
Leeds, 2. NORMAN LISSIMORE.

Long-term Anticoagulant Therapy

SIR,—Dr. G. R. Fearnley's letter (*Journal*, April 25, p. 1115) is long and learned but seems to me to be based on a fallacious assumption. It is, I submit, not impossible for general practitioners to draw off 2 ml. of blood for estimation of the prothrombin efficiency. It is not therefore necessary for every patient requiring anticoagulant treatment to be admitted to hospital; nor, if long-term anticoagulant treatment is required, need the time and patience of both consultants and patients be wasted by constant attendance at specialist clinics for this purpose.—I am, etc.,

South Chailey, Sussex. J. R. CALDWELL.

SIR,—The report to the Medical Research Council of the controlled therapeutic trial (*Journal*, March 28, p. 803) is open to serious criticism in at least one respect. Having found that deaths were somewhat more frequent among the low-dosage group than among the group receiving high dosage, the authors proceed to add to the deaths those patients who were withdrawn from the trial because of severe recurrent infarction or cardiac failure. When they do this, they are likely to exaggerate the difference between the two treatment groups for the following reason.

If a patient receiving high dosage of anticoagulant sustained a further myocardial infarction, his physician would normally have proceeded with high dosage anticoagulant therapy. On the other hand, a patient developing a severe recurrent infarction while on low dosage might readily have been taken out of the trial in order to be put on to high dosage treatment. We imagine that this is what is implied by the statement relating to the nine patients with recurrent infarction whose "physicians removed them from the prescribed trial regime and treated them in a more flexible manner." It is therefore illogical to add to the deaths those cases withdrawn from the trial because of severe recurrent infarction. These all occurred in the low-dosage group, none being withdrawn for this reason from the high-dosage group. We submit that to lump together the deaths and the withdrawal for this particular reason as "failures in prophylaxis or treatment" is an example of the use of biased data.

We believe that the withdrawals because of severe recurrent infarction are more likely to reflect the opinion of the physician that severe recurrent infarction must be treated with anticoagulants in full doses than to constitute valid data for comparing the two treatment groups. Our belief is strengthened by the flat statement which opens your leading article in the same issue (p. 838) that "The value of treatment with anticoagulants during the first four weeks after acute myocardial infarction is now established."

With a common disease which causes many deaths, the criterion above all to judge the efficacy of prophylactic treatment should be death. In this particular study the difference in deaths in the two groups is no more than suggestive. A useful secondary guide is the frequency of recurrent infarction. In this study the total reinfarction rate was significantly higher in the low-dosage group. However, the diagnosis of a recurrent infarction is sometimes difficult, and we therefore agree with Professor John McMichael (*Journal*, April 11, p. 970) that it is unfortunate that the criteria by which the occurrence of reinfarction was judged were not defined in the report, especially as the physicians knew the treatment group to which the patients belonged.—We are, etc.,

G. E. HONEY.
S. C. TRUELOVE.

The Radcliffe Infirmary,
Oxford.

The Oestrogens

SIR,—We read with interest Dr. G. I. M. Swyer's article "The Oestrogens" (*Journal*, April 18, p. 1029), and as we have recently carried out some trials on the treatment of the climacteric we venture to put forward some of our experiences with the preparations Dr. Swyer mentions.

Our patients consisted of 40 women with marked and multiple menopausal symptoms, who were attending Dr. Peter Bishop's endocrine clinic. None of our cases could be classed as mild, which may be the reason why we found only 5% could be kept contented on 0.5 mg. stilboestrol (or the equivalent dose of dienoestrol) daily. Admittedly, it is possible in many cases to reduce as against control their hot flushes with doses of 0.2–0.5 mg., but there is no sense of "well being," and other symptoms such as morning lethargy, irritability, insomnia, depression, etc., remained unchanged.

We now have become convinced that it is essential to control all their symptoms as quickly and as effectively as possible and so gain their confidence. In severe cases this was best achieved by either an injection of 5 mg. oestradiol diproprionate or 12 mg. chlorotrianisene ("tace") daily. The former is usually effective within 48 hours and the latter within 3 to 5 days. Furthermore, we found one dose of 5 mg. oestradiol dipropionate remained effective for an average of three weeks and was longer acting than 10 mg. oestradiol valerianate. We agree with Dr. Swyer that one or two courses of chlorotrianisene did not bring about a "cure," nor did we find much evidence of a storage factor, but most patients felt very well while taking it. Satisfactory results were also obtained with methallenoestril ("vallestril"), but in the majority of patients it was necessary to commence with a daily dose of 9 mg. In selected cases where nervous irritability was a major factor we have had good results with a combination of ethinyl oestradiol and meprobamate (now under the trade name of "equadiol").

We would also like to add that we have found the use of vaginal cytology of the utmost help in dealing with these patients. It not only assists in the original assessment (we have never seen a post-menopausal woman with symptoms who had an oestrogenic smear), but it is a most useful therapeutic guide. There is no doubt that women vary in their ability to metabolize these oestrogen preparations adequately, and when the clinical response is poor we have found this to be borne out by their vaginal smears in all except one case, which was referred to a psychiatrist.—We are, etc.,

FREDA OSMOND-CLARKE.
MOIRA MURRAY.

Chelsea Hospital for Women, London, S.W.3.

Cortisone and the Acute Red Eye

SIR,—Mr. J. D. Abrams's letter (*Journal*, April 25, p. 1116) deserves wide publicity, and I wish to support his plea for caution in the use of corticosteroids in inflamed eyes. There is no doubt that healing is delayed in some cases and that the whitening of the eye resulting from cortisone may be misleading. It is particularly in dendritic (herpetic) ulceration that these drugs present their gravest risk and are actually damaging.

The general practitioner is in a difficulty here. He is not willing to send his patient unnecessarily to an overburdened eye department, and yet he may not possess the facilities and experience to make a definite diagnosis. It would, I think, be unrealistic to advise practitioners to avoid the use of cortisone unless the patient had been seen by an oculist, but it would be reasonable to say, "Unless you can be *certain* of the integrity of the cornea, keep off cortisone."—I am, etc.,

Edinburgh, 3. C. R. S. JACKSON.

SIR,—I was interested to observe Dr. J. D. Abram's comments on "Cortisone and the Acute Red Eye" (*Journal*, April 25, p. 1116). As a general practitioner myself I would agree that, armed as many of us are with a somewhat slender knowledge of ophthalmology, the temptation to use such an attractively effective panacea as cortisone, in order to compensate to some degree for our therapeutic void, is great. A recent case of mine deserves mention in this respect.

A young lady, aged 17, developed a severe bilateral facial herpes simplex, affecting particularly the right eye, which was completely closed by marked oedema of the eyelids with periorbital cellulitis. She was toxic, febrile, and in considerable pain. After three days' treatment with systemic penicillin, and local treatment to the eyelids including the use of oculent. neomycin., the cellulitis was relieved, her general condition improved, but the eyelids remained closed and oedematous. As it was considered that the cornea had also been involved by the herpes virus and the pain would persist until carbolization could be done, I prescribed oculent. hydrocortison. et neomycin. to the lids, and after 48 hours the swelling was reduced sufficiently for the patient to open her eye, a red eye and a dendritic ulcer being clearly visible. This treatment was continued, applying the ointment into the eye in addition until she was seen at hospital the next day, where the ulcer was cauterized, and the local treatment continued, with addition of a mydriatic, the application of which was now possible. The subsequent recovery has been slow and punctuated by recrudescences of activity requiring further cauterization. The condition has almost subsided now some four weeks after its start.

No doubt this case may illustrate Dr. Abrams's point to a certain degree; but I wish to submit my plea for leniency in his judgment; for I submit that the rapid relief of the condition of the eyelids obtained by the use of cortisone more than justified the fact that its use in virus ulcers is generally contraindicated. If there is any other way of expediting this effect, I am unaware of it.—I am, etc.,

Southgate, N.14. DAVID B. FOX.

Venous Shunts in Cirrhosis

SIR,—I wish to point out that it has been necessary for your leader writer (*Journal*, April 11, p. 963) to distort the figures published in my monograph on portal hypertension[1] to show that Nachlas's article[2] is "not unduly pessimistic." The relevant paragraph (p. 106 *et seq.*) should be paraphrased or quoted as follows:

In advanced cirrhosis, 23 out of 110 patients had shunt operations and "included are four early patients, Nos. 2, 5, 9, and 11, operated on in 1948 and 1949, who would not at present have been considered suitable for operative treatment." In addition two died of intercurrent disease with patent anastomoses, and one of carcinoma of the bronchus with a thrombosed shunt. Nine died of liver failure, but 7 of the 23 survived in good or reasonable health. By contrast, of the 60 of the 110 patients in this group who had had no operation, only 5 survived in reasonable health with medical treatment alone at the time of the analysis; 5 were deteriorating; 3 had bled since the analysis had been completed and had had porta-caval anastomosis, with one death; 47 were dead.

On the whole, therefore, these figures do not contra-indicate occasional shunt operations even in this, the least favourable group. It is agreed that the advanced cirrhotic who bleeds is in a desperate state. That surgeons have attempted too much in finding out which patients can tolerate an operation to prevent haemorrhage is no reason to quote the figures to support an opposite point of view. Your leader-writer ignores the excellent results obtained in the groups of mild and moderate cirrhotics.

To refer back to Nachlas's article, your writer states that "his method was to ask a number of highly pertinent questions and answer them from information recorded in the literature." The degree of selection that has been exercised in setting forth this information so that it supports his theories is remarkable. Nobody familiar with portal and splenic venography, the degree of diversion of portal blood flow in portal obstruction, and the interrelationships between the complex state that results from such an obstruction and the extent of portal venous hypertension before and after shunt operations, would have failed to realize that many of

the questions Nachlas raises have already been answered. That many workers in this field are not Americans may account for Nachlas's surprising omissions. From my own point of view I was interested to see that he quoted a brief note I wrote as early as 1949 to support his opinion and ignored all subsequent publications in which I have made an attempt to answer some of the questions posed by this complex condition.

I agree wholeheartedly with Professor R. Milnes Walker's opinions and statements in his letter (*Journal*, April 25, p. 1118). Your postscript to his letter suggests to me that your leading article should not have been written until after publication of the experiment planned by the Veterans Administration. Lastly, I should be very pleased to invite the anonymous writer of your leading article to attend my monthly follow-up clinics for portal hypertension and see the results of treatment for himself. Most of the patients will have been treated surgically, some as long as 10 years ago.—I am, etc.,

St. Bartholomew's Hospital, London, E.C.1. ALAN H. HUNT.

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Human Fascioliasis

SIR,—Dr. R. Vaughan Facey draws attention (*Journal*, April 25, p. 1115) to the occurrence of human fascioliasis in Hampshire, and it may very well be, as he says, that the infection is more likely to occur after a succession of wet summers. This was certainly the experience in recent outbreaks in France.

I have encountered five human cases of this infection since 1951, and the clinical features were similar to those noted by Dr. Vaughan Facey. All the cases had enlargement of the liver giving rise to considerable pain, pyrexia, either continuous or intermittent, with rigors in some instances, asthenia, loss of weight, and sweating, and in every one of my cases a high degree of eosinophilia was present.

In the three most recent cases, which occurred at the same time towards the end of 1957, the ova were found in all, but they did not appear in the faeces until three months after the infection commenced. While watercress appeared to be the infecting agent in four of the cases, in the fifth none had been consumed, but the patient was in the habit of chewing grass.

The diagnosis is certainly not an easy one, and three of my patients were subjected to laparotomy. I failed to make the diagnosis in my first patient and subsequently referred her to Dr. Kenneth Harris at University College Hospital, and I am indebted to him for making me aware of this condition, which may be more common than we think. Most references to the condition in our literature are of cases diagnosed at operation for suspected gall-bladder disease, but a very good account of a case was recorded many years ago by Dr. S. W. Patterson,[1] of Ruthin Castle.—I am, etc.,

Porthcawl. F. L. DYSON.

REFERENCE

1 Patterson, S. W., *Lancet*, 1928, **2**, 1291.

Dystonic Reaction to Trifluoperazine

SIR,—The accounts of dystonic reaction to perphenazine recorded in recent issues (*Journal*, February 7, p. 368; March 28, p. 859) prompt me to report two cases of a similar reaction to trifluoperazine ("stelazine").

A physically healthy married woman, 28 years of age, was receiving out-patient psychiatric treatment for tension headaches of ten years' duration and was given 5 mg. of trifluoperazine twice daily. Twelve hours later when she had taken 10 mg. she noticed that the muscles in the front of her neck and jaw were becoming very stiff, and this stiffness spread to involve all the muscles of her neck, which was held in an extended position with her jaw thrust forward. The spasmodic condition of the muscles spread backwards and to the left side to involve the muscles around the left shoulder. The dystonia was almost constant, but there were periods of relaxation. The condition subsided after about six hours; the muscles involved remained tender on palpation for two weeks.

Another patient, an 18-year-old girl in good physical health, who was also receiving out-patient psychiatric treatment for a severe anxiety neurosis of recent origin, was given the same dose of trifluoperazine, and she developed a similar group of symptoms, but in her case the spasmodic condition was confined more to the muscles at the back of the neck and the symptoms were less intense. When the drug was withdrawn the symptoms subsided completely, leaving no residual tenderness.

—I am, etc.,

East Glamorgan Hospital, Near Pontypridd. T. S. DAVIES.

Rubella in Pregnancy

SIR,—I am rather surprised to see that none of your correspondents has commented on the position (presumably arranged with editorial intention) of Dr. Julia Bell's interesting article on rubella in pregnancy (*Journal*, March 14, p. 686). The succeeding article was "Deaf or Dead." Unfortunately one cannot consult the foetus. In any case, how many of the 421 defects listed are really incompatible with a future useful and happy life?—I am, etc.,

W.H.O. Regional Office for Europe, Copenhagen. J. D. COTTRELL.

SIR,—Dr. Julia Bell, in discussing rubella in pregnancy (*Journal*, March 14, p. 686), has certainly turned the clock back when she states, "abortion has become the generally recognized treatment in such a case." This may have been true 10 to 15 years ago, when Swan's misleading figures suggested that congenital malformation was almost inevitable after rubella in early pregnancy. Since then it has become generally agreed that his retrospective observations gave a false picture, and later observers, using prospective methods, have almost without exception shown a low malformation rate. These include Ingalls, 15.9%[1]; Greenberg, 9.7%[2]; Dumont, 9%[3]; Bradford Hill, 20%[4]—all for the first trimester. In my own current series, at present of 50 cases, a provisional risk figure is 10%—that is 90% of the children so far appear to be normal.

Moreover, in other teratologies, the malformation rate is usually low. At Hiroshima the incidence of microcephaly with mental retardation, due to the atomic bomb irradiation effects in the first 15 weeks of pregnancy, was 20%.[5] In experimental malformations, where deliberate "insults" are applied to the early embryo, the percentage of abnormal offspring is again often not high. For example, Ingalls,[6] repeating Stockard's work on anoxia applied to fish embryos, was not able to malform more than 21% of the offspring, even under the deliberate conditions of the laboratory.

All these observations show that in the past we have talked too much about the *vulnerability* of the embryo to noxious influences, and not enough about its *resistance*, its inherent drive towards normality, which may be difficult, and not easy, to disturb. It seems clear that a human embryo that has been exposed to maternal

rubella still has a 80–90% chance of developing normally, provided it is not eliminated by the "treatment" that Dr. Bell advocates.

Her paper is disappointing; her cases are drawn from weighted sources, often retrospective; documentation is absent, and, like Swan, she presents a picture heavily biased with abnormal cases. Moreover, her statement quoted above is incorrect, as termination of pregnancy for rubella has been practically abandoned in many parts of the world, where more enlightened opinion, recognizing the embryo's strong drive towards normality, permits it to flower to term.—I am, etc.,

DAVID B. PITT.

Department of Obstetrics and Gynaecology,
University of Melbourne, Australia.

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1 Ingalls, T. H., *Amer. J. Dis. Child.*, 1957, **93**, 555.
2 Greenberg, M., and Barton, J., *J. Amer. med. Ass.*, 1957, **165**, 675.
3 Dumont, M., *Gynéc. et Obstét.*, 1957, **56**, 99.
4 Hill, A. B., Doll, R., Galloway, T. McL., and Hughes, J. P. W., *Brit. J. prev. soc. Med.*, 1958, **12**, 1.
5 Miller, R. W., *Pediatrics*, 1956, **18**, 1.
6 Ingalls, T. H., and Philbrook, F. R., *New Engl. J. Med.*, 1958, **259**, 558.

SIR,—I have not seen mentioned yet one obvious objection to Dr. Julia Bell's idea of aborting every case of German measles which occurs in the first three months of pregnancy (*Journal*, March 14, p. 686). Altogether, apart from the ethical side and the lack of evidence to support her conclusions, in how many cases can one be absolutely certain that the mother has got rubella, and not a mild English measles, glandular fever, "fourth" disease, or any one of the many other morbilliform rashes?

There is at present a mild epidemic of measles, German measles, and glandular fever in this area, and even the most experienced of us cannot always separate them for certain. Her whole thesis seems untenable.—I am, etc.,

Herne Bay. QUENTIN EVANS.

SIR,—Some years ago Sir Edward Mellanby asked me to investigate this problem, but I met with so much emotional bias and even hostile reaction to any inquiry into the facts that I refused to pursue the matter. Apparently nothing has changed in the interval. In the meantime facts have accumulated owing almost entirely to the pioneer work in Australia and later in America.

I have nothing to add to my note (*Journal*, March 14, p. 686), but ask that critics should abstain from misinterpreting the summary of my statistics, which are completely adequate for the limited purposes for which they were used. I resent their being described as "unreliable"; they are after all based for the most part on notes by doctors on cases under their care, and in some respects present a much more illuminating picture than do routine facts collected by an impersonal observer.

There are three main aspects of this problem concerned with (*a*) the risks of severe handicap to the unborn child, (*b*) the risks of acute distress and difficulty for the potential parent, perhaps for the rest of her life, (*c*) the burden likely to rest upon the Welfare State. I appreciate the difficulty in reaching a decision in certain cases, but these must be very rare and do not touch the main problem. I would remind my critics that the purpose of my note was to suggest a period of pregnancy beyond which an attack of rubella appears to constitute no serious risk to anybody.

A large-scale farmer in Kenya tells me that, when his pregnant cows with virus disease abort, he notes a tendency for them to become sterile. I should be glad to hear of any observations relating to subsequent pregnancies in women who have miscarried whilst pregnant with a history of rubella.—I am, etc.,

The Galton Laboratory, JULIA BELL.
University College London,
Gower Street, London, W.C.1.

Diagnosis of Multiple Pregnancy

SIR,—When confronted by the problem of the pregnant woman who in the last six weeks of her pregnancy has a uterus larger than the duration of pregnancy would indicate, I have found the palpation of the loins a helpful test. The presence of foetal parts in one or both loins would seem to be an indication of multiple pregnancy. I would be interested to know if other practitioners have had the same experience.—I am, etc.,

Liverpool, 23. J. MALCOLM ABBOTT.

Physiotherapy in Arthritis

SIR,—To an industrial medical officer who has to cope daily with the results of wear and tear, stance and posture and stress, especially in repetition tasks, it is refreshing to find an authority like Dr. James Cyriax (*Journal*, March 28, p. 857) saying plumb and plain that the four common forms of physiotherapy are useless in arthritis. Patients themselves are, I find, increasingly aware of this conclusion, and are increasingly inclined to say that the people who could do them some good—the orthopaedic surgeons and their assistants—cannot be bothered to do so. When the conclusions of Professor E. G. L. Bywaters, Miss D. E. Hamilton, and Mr. N. W. Please (*Journal*, February 28, p. 542), and now of Dr. James Cyriax, have been digested and accepted, we may hope to get greater reliance on passive movements and graduated active movements, manipulative correction of subluxations, and pressure upon nerve roots, combined with massage. Pain and disabilities of feet and hands, and conditions of chronic strain in ankles and knees, appear to be not sufficiently treated.—I am, etc.,

Rushden, Herts. E. H. STRANGE.

SIR,—Miss D. E. Hamilton, Professor E. G. L. Bywaters, and Mr. N. W. Please (*Journal*, February 28, p. 542) have recently discussed the results of "A Controlled Trial of Various Forms of Physiotherapy in Arthritis." The treatments selected were short-wave diathermy, infra-red irradiation, wax baths, and faradism to the quadriceps; each treatment was given for 20 minutes three times a week, for one month in turn, and contrasted with a dummy treatment. All of the 131 patients selected were on a "basic regime" of active exercises, "analgesics as required," and "splintage as necessary," and only 67 patients completed the five-months trial. The authors were unable to show that these additional physical treatments had any measurable effect on joint function or muscle power in a miscellaneous group of patients with rheumatoid arthritis and degenerative joint disease, whose age, sex, and disability were not even specified. What did they expect? A similar "controlled trial" substituting 10 gr. (0.65 g.) of aspirin thrice weekly for palliative physiotherapy would most probably yield equally disappointing results, since local heat, whether given by short-wave diathermy,

infra-red irradiation, or wax baths, is only intended as an analgesic prior to the exercise of stiff and painful joints. It can scarcely have a measurable effect on a disease such as rheumatoid arthritis. Faradism is rarely prescribed, except to educate a patient to use muscles weakened by disuse, or to strengthen such muscles when voluntary contraction is inhibited—for example, by pain.

It seems clear that this "controlled trial" of physiotherapy has proved nothing. In addition the remarks in the opening paragraph criticizing the lack of such trials are misleading, and the authors have perhaps overlooked such papers as those by Curwen and Scott[1] and Millard and Wynn Parry.[2]

Dr. James Cyriax (*Journal*, March 28, p. 857) claims that none of these treatments has any lasting effect on any form of arthritis. Does any treatment have such an effect, with the possible exception of bed-rest, weight reduction, and chrysotherapy? No doubt useless physiotherapy is still prescribed and administered, but since the war many traditional forms of physiotherapy, such as long-wave diathermy and iontophoresis, have all but disappeared, whilst hydrotherapy is now limited more and more to exercises in the warm pool. Greater emphasis is placed on splintage, exercise, and assistance with the activities of daily living in departments of physical medicine.

The statement by Dr. Cyriax, "I trust that this timely article will begin the deliverance of the trained physiotherapist from a mass of useless work," is presumably prompted by the wish that the physiotherapist should devote more time to equally empirical and possibly more dangerous methods of treatment. Local heat in any form, even if given prior to exercise, may well be a waste of time and money; what statistical evidence have we that analgesics, splints, exercise, manipulations, or even visits to the doctor are any better?—We are, etc.,

A. C. BOYLE.
S. MATTINGLY.

Department of Physical Medicine and Rheumatism,
The Middlesex Hospital, London, W.1.

REFERENCES

[1] Curwen, I. H. M., and Scott, B. D., *Ann. phys. Med.*, 1952, **1**, 17.
[2] Millard, J. B., and Wynn Parry, C. B., ibid., 1953, **1**, 156.

Steroid Metabolism in Congenital Adrenal Hyperplasia

SIR,—Apropos the admirable treatise by Dr. C. L. Cope (*Journal*, March 28, p. 815), in view of the citation of our work I should like to clear up some possible misunderstanding.

I do not believe that the results contradict the deficiency of various hydroxylases in this syndrome, and feel that our long persistent study of this problem supports such a defect. I write principally to clarify our position on the degree of block, since it would appear that we have always proposed a "complete" interference with hydrocortisone biogenesis in the adrenogenital syndrome due to congenital adrenocortical hyperplasia. As early as 1954 we stated[1] in our summary that "the defect in biosynthesis is not complete." Since then we have published many results in support of partial deficiency, and, while Dr. Cope may not have intended to create a misinterpretation of our earlier work, his publication has evidently conveyed this impression, since other readers have made inquiry of us on this very point.

I should like to add that unpublished data of Fukushima and Gallagher, of the Sloan-Kettering Institute, New York, clearly indicate that patients with this disorder do not dispose of administered isotopic hydrocortisone in a manner different from usual.—I am, etc.,

ALFRED M. BONGIOVANNI.

Paediatric Endocrine Research Division,
University of Pennsylvania.

REFERENCE

[1] Bongiovanni, A. M., Eberlein, W. R., and Cara, J., *J. clin. Endocr.*, 1954, **14**, 409.

Results of Cancer Education

SIR,—I read with great interest the assessment of results from cancer education which is being carried out in the Manchester area (*Journal*, March 14, p. 708) and was pleased to see that the figures suggest that nothing but good is resulting from the experiment. I would, however, suggest that the method of evaluation started in 1953 in the East Riding of Yorkshire under the auspices of the Yorkshire Council of the British Empire Cancer Campaign might be added to the present method of assessment.

The object of cancer education is not to teach the public how to diagnose cancer but to encourage patients to go to the doctor when he or she notices certain symptoms, *whatever the cause may be*, and it is therefore essential to find out if the delay in reporting these symptoms is becoming less. For this purpose, in Yorkshire, one clerk in each of four hospital record departments was given the duty of registering all patients who came to the hospital with those symptoms, whatever the cause, and to record the delay between the time the symptom was noticed and the first visit to the doctor. The symptoms selected were lump in the breast, uterine bleeding, rectal bleeding, haematuria, hoarseness of voice, lump or ulcer of the tongue, mouth, lip, skin, or vulva.

At the end of each six months a complete list of patients registered and the delays were sent to me to analyse under the heading of each of the symptoms. These of course included some cases proved to be cancer, and they were further analysed. The results of the analysis were expressed by a "group percentage method"—i.e., the number of patients seeking advice in less than one month, 1 to 2, 2 to 3 months, etc., and the numbers were expressed as a percentage of the total number registered under that symptom. After three years the hospital board took over cancer registration, and I regret that the method was no longer continued.

During the three years 6,944 cases were analysed. There was not in so short a time any definite statistical evidence of any increase in the number reporting in less than one month, but there was a suggestion that the number of long delays—i.e., two years or more—had a downward trend. Rectal bleeding was a good example. At the end of the first six months the percentage of over two years' delay was 38.3%, but it steadily decreased and in the last analysis was 7.6%. It was also interesting to note that each symptom had its own percentage pattern each six months. For example, the percentage of patients reporting haematuria in the first month was high, sometimes 70%, but uterine and rectal bleeding was always low.

If this method could be carefully carried out then a diminution in the delay in reporting certain symptoms, whatever the cause, and a rise in the number of early stage cancers treated would prove the value of cancer education. Unfortunately the stage of the disease when treated was rarely recorded in the Yorkshire hospitals.

Everybody will agree that "informal talks" are more effective than newspaper and other printed publicity, and I congratulate Mr. Wakefield on the splendid work he is doing for the Manchester cancer committee, but the

number of people who are willing to give such talks is small. I am convinced that the nursing profession, acting under the medical officers of health, can put across a great deal of information about cancer if they are coached in doing it. They are the friends of the people and in a better position than anybody else to carry out this work.—I am, etc.,

Oxford. MALCOLM DONALDSON, Honorary Secretary, Cancer Education Association.

Geographical Tongue

SIR,—A female patient, aged 38, has had "geographical tongue" for some years, and, as is common with this syndrome, treatment has been of no avail. Recently she had a week's course of erythromycin (in the form of "filmtabs" containing erythromycin stearate) for a penicillin-resistant staphylococcal bronchitis. At the end of the week's course her tongue was completely free from markings for the first time for some years. The circular lesions started to reappear as soon as the drug was withdrawn. Dummy filmtabs were obtained from the makers (Abbott Bros.) and a full course given a month later without effect.

As the aetiology of this condition is not known, perhaps this observation may be of interest.—I am, etc.,

Newent, Glos. K. M. TOMLINSON.

Herpes Zoster during Steroid Therapy

SIR,—Dr. G. E. Breen's letter in the *Journal* of April 18 (p. 1039) on the action of corticoids in herpes zoster was very informative. However, lest somebody may be tempted to use steroids in severe herpes zoster for the purpose of producing an improved result, I should like to mention a recent experience with corticoids in this disease. I treated a patient with prednisolone for a severe attack of rheumatic fever. While she was on treatment she developed herpes zoster. The herpes took about two months to heal and the resulting scar was the most unsightly that I have ever seen.—I am, etc.,

University, College, Galway. B. J. O'DRISCOLL.

Catching Up with Cabot

SIR,—As regular readers of both the *New England Journal of Medicine* and the *British Medical Journal* we were gratified to learn of your intention "to follow the example of our New England colleagues in Boston" and publish a series of clinico-pathological conferences (*Journal*, January 24, p. 220). Moreover, we were pleased to see the excellent conference in the same issue (p. 224), which Professor Robert Platt handled in the true Cabot tradition.

As you rightly state in your introductory leading article: "Much of the educational value of these conferences depends . . . on the candour and fearlessness of the participants. The clinician . . . who in discussion is prepared to chance his arm, confess ignorance, or air a doubt gives a wholesome example to his colleagues." This, we feel, is the whole point of a "Cabot conference." A clinician previously unacquainted with the patient is confronted with the case history and laboratory findings, from which he is expected to present a coherent account explaining the course of the patient's illness and anticipating the pathologist's report so far as clinical acumen will permit.

With this in mind, it was disappointing for us to read your two more recent conferences, "A Complicated Case of Cirrhosis" (*Journal*, February 28, p. 568) and "A Case of Subacute Bacterial Endocarditis" (*Journal*, March 28 (p. 844). In the first place, what we feel is the most important feature—the clinician's assessment—is wholly absent from both reports; secondly, the diagnoses are given at the beginning, thus spoiling all the natural dramatic interest of the cases. The modification of these two features completely destroys the conferences as effective teaching devices and relegates them to the status of mere case reports, which might have been written in a much shorter space.—We are, etc.,

ROBERT FORTUINE. MARY SZWARC.
PAUL DYMENT. PHILIP SEEMAN.
HUGH ROBSON.

McGill University, Montreal. Medical Students.

Invalid Vaccination Certificates

SIR,—I was delighted to see the recent correspondence, begun by Dr. I. J. Corbett (*Journal*, March 7, p. 644), relating to invalid vaccination certificates, as it gives me an opportunity to bring up another aspect of vaccination certificates. Regularly medical practitioners in this area are faced with requests for vaccination — of business executives, mining students, families of miners going overseas to join their husbands, and the like—and always in a hurry. And there arises, equally regularly, the question as to where the "International Certificate of Vaccination" may be obtained.

We are told by Mr. S. A. Heald (*Journal*, March 21, p. 790) that the main travel agencies will produce them. Very frequently, however, booking is done in London —either by the firm employing the businessman or the head office of the mine—and in the bustle of getting away the prospective traveller does not receive a blank certificate, about which he could not care less. All of which leaves the wretched G.P.—who knows very well what a to-do will arise later in the absence of the proper certificate—scratching around and trying his blandishments on the local travel agencies in an effort to avert trouble from his patient later on. It does seem a little absurd that we who are responsible for the proper carrying out of vaccination should not have access to the proper forms.—I am, etc.,

Camborne, Cornwall. W. F. CASTLE.

Collection of Pneumothorax Apparatus

SIR,—There is being formed at the Wellcome Historical Medical Museum a collection of pneumothorax machines and needles illustrating the various models from the time of the first Forlanini instrument to those invented in the 1940's. The nucleus of this collection is at present in Leeds and will be shown, before its transfer to the Wellcome Historical Museum, at a meeting of the British Tuberculosis Association and the Yorkshire Thoracic Society in September, 1959. The present collection is nearly complete as regards English models of machines and is complete as regards English needles.

If any of your readers have Continental, British, or American apparatus that is no longer required, I would be grateful for their loan for the Leeds exhibition; or their gift for the same reason prior to their transfer to the permanent collection to be kept in London.—I am, etc.,

Killingbeck Hospital, York Road, Leeds, 14. THOMAS MARMION.

Obituary

WILLIAM AINSLIE, *M.C.*, M.D., F.R.C.S.Ed.

Dr. William Ainslie, a notable figure in the medical and public life of Herefordshire, died at his home in Hereford at the age of 82. He was consultant surgeon to a number of hospitals in Hereford.

Born at Stobo, Peebles-shire, on July 27, 1876, William Ainslie entered the medical faculty at Aberdeen University at the age of 15, and graduated M.B., Ch.B. in 1897 at the age of 21. He had his first practical experience as assistant for a year in a large colliery practice in South Shields, after which he entered general practice at Kington, Herefordshire. He remained in that practice until 1910, and his name is still remembered by many of the older people there for his medical ability and kindness, and also for his prowess on the cricket field. His growing interest in, and aptitude for, surgery led him to leave Kington for Edinburgh, where he spent two years, taking his F.R.C.S.Ed. in 1911 and preparing a thesis which gained him his M.D. in 1913. He returned to Herefordshire in 1912 to join Dr. Edgar Morris in practice in Hereford city, but the outbreak of the first world war in 1914 took him into the R.A.M.C., in which he served until 1918. He saw active service in the trenches of the Western Front, was wounded, and was awarded the Military Cross in 1917. On his return to practice in Hereford he lived a very full life, taking a leading part in medical and local affairs for many years. He was president of the Worcestershire and Herefordshire Branch of the B.M.A. in 1926–7.

C. W. W. writes: The death of Dr. William Ainslie will be felt with real sorrow by a very wide circle of friends. His quiet manner, complete lack of affectation, gentleness, and unfailing good humour inspired deep and lasting affection in those he met, while his professional qualities gained for him widespread confidence and respect.

At Hereford after the first world war he entered upon a practice remarkable even then and almost incredible from a modern standpoint for its range and versatility. He was and remained a general practitioner, but soon became a surgeon at Herefordshire General Hospital, in addition to his post as radiologist to that institution. He had to tackle all branches of surgery—internal, orthopaedic, ear and throat, as well as midwifery and gynaecology—and did so with efficiency and success until, with the increasing specialization of modern medicine, one branch after another was separated as a special department. In his active years his life was spent in unremitting work in the operating theatre, the *x*-ray department, the homes of his patients, and in consulting work which took him from end to end of the county and beyond its borders. Often his car would be loaded with instruments, sterile drums, and anaesthetic kit, or with his portable *x*-ray apparatus, which was supplied with power by a dynamo linked to the engine of his car. His notable talent for midwifery was fully realized by his professional brethren, and his services were in constant demand for their more difficult obstetrical problems. In spite of all these activities, Ainslie—I should say William or Bill, for he was known and affectionately spoken of by his Christian name by all who knew him—always had time to listen to anyone who came to him and to stay and chat after the medical situation had been dealt with.

Such a life would have been impossible without the help and forbearance of a remarkable wife, and much of the credit for his success must be accorded to Mrs. Ainslie for her help and sympathetic interest in all his undertakings. Together they had to bear in 1936 a bitter sorrow when their daughter, Nita, met her death in tragic circumstances in the Sahara Desert. Both Dr. and Mrs. Ainslie were deeply interested in the affairs of the city of Hereford. Mrs. Ainslie served for years on the city council and eventually became mayor of the city. In 1952, on the resignation of Sir John Arkwright, the city council unanimously elected William Ainslie to the ancient and honourable dignity of Chief Steward of the city of Hereford. Only a week before his death he took part in the ceremony of presentation of the freedom of the city to the R.A.F., in the course of which he had to read the ancient charge to the recipients of this honour.

He died after two days of illness, and is mourned by his widow and two sons, Ronald, a solicitor, and Derek, ophthalmic surgeon to the Middlesex Hospital.

J. ERNEST WALKER, M.B., Ch.B., D.M.R.E.

Dr. J. Ernest Walker, consultant radiologist to the General Hospital, Burton-on-Trent, died suddenly at his home at Derby on March 29 after a period of ill-health. He was 63 years of age.

John Ernest Cuthbert Walker was born on July 25, 1895. After serving in the first world war he qualified as a pharmacist and then turned to medicine, graduating M.B., Ch.B. from Liverpool University in 1925. He took the Liverpool D.M.R.E. four years later. After graduation he held appointments at the Royal Southern Hospital and the Mill Road Infirmary, Liverpool, and at Townley's Hospital, Bolton. Entering general practice at Hazel Grove, Cheshire, in 1932, he built up a busy practice and remained there until 1944. After postgraduate study at Hammersmith, he took up a radiological appointment at the North Staffordshire Royal Infirmary, Stoke-on-Trent. In 1947 he was appointed to the staff of the General Hospital, Burton-on-Trent, as its first consultant radiologist. Under his direction the radiological department was altered and enlarged to enable it to cope with the constantly increasing volume of work.

Dr. Walker's many fine qualities were greatly appreciated by his colleagues and friends, to whom on all occasions he was most helpful. An extensive knowledge and wealth of experience made his opinion and advice invaluable, while his kind and considerate attitude to patients was most reassuring. His wife, who was a member of the nursing profession, predeceased him by two months, and her ill-health had been a source of great anxiety to him. To his family we tender our deepest sympathy and hope that they, in their sorrow, will find a measure of relief in the knowledge of the high regard and esteem in which their father was held. His only daughter is a student nurse, his elder son a member of the police force, and his younger son is an undergraduate of Emanuel College, Cambridge.—H.T.C.

J. R. GARROOD, M.D., D.P.H.

Dr. J. R. Garrood died at his home at Alconbury Hill, Huntingdon, on April 22. He was 85 years of age.

Jesse Robert Garrood was born on March 1, 1874, the son of Mr. Jesse Garrood, of Ledbury. From St. John's College, Cambridge, he went on to St. Thomas's Hospital to receive his clinical training. He graduated M.B., B.Chir. in 1899, and immediately entered rural general practice with Dr. Lancelot Newton at Alconbury Hill, Huntingdon. He took the Cambridge D.P.H. in 1900 and proceeded to the M.D. four years later. In 1902 he married Miss Janet Newton, his partner's daughter, and thereafter, apart from a period with the R.A.M.C. during the first world war, spent his whole life at Alconbury Hill. He succeeded his father-in-law as medical officer of health to the Huntingdon Rural District Council in 1924, and with him spanned a period of over sixty years in the public health service. He retired in 1958. A member of the British Medical Association for fifty-eight years, he was chairman of the Cambridge and Huntingdon Division in 1922, and president of the Cambridge and Huntingdon Branch in 1929–30.

J. K. P. writes: Dr. J. R. Garrood was an archaeologist of considerable erudition, the author of a small book on the subject, and was honoured by election to the fellowship of

the Society of Antiquaries. In his sixty years in Huntingdonshire he became very much a part of the community, and many will miss his agile brain and blunt speaking, his intensely inquiring attitude towards all aspects of human ecology, his delight in motoring and photography, and above all his rugged individuality. There will be many who will grieve and join in offering their sympathy to his widow.

K. B. THORNTON, M.D., M.R.C.P., D.C.H., D.A.

Dr. Kenneth Thornton, a general practitioner in Liverpool, died at his home on April 13, the day before his 44th birthday.

Kenneth Bruce Thornton was born in Bromley, the son of Arthur Bruce Thornton. After his early education at Cottesmore and Lancing College he went on to St. Thomas's Hospital, and graduated M.B., B.S. from London University in 1938. There followed a period of house appointments and clinical assistantships in obstetrics and gynaecology, tuberculosis, and general medicine. He showed an early interest in anaesthetics and took the D.A. in 1940, having already obtained the primary F.R.C.S. as a medical student.

Like many of his generation, Kenneth Thornton's career was interrupted by the second world war. He volunteered for the Army in 1940 and had a short period with a Signals unit. His anaesthetic qualifications, however, brought him to a specialist surgical unit and with this he went to the Far East in 1942. He soon left this unit to volunteer for service with a parachute surgical team and took part in the operations which culminated in the capture of Rangoon and during which he received a leg wound. On demobilization in 1946 he discovered an interest in paediatric medicine and spent a year at St. Thomas's and the Queen Elizabeth Hospital for Children. He proceeded to the M.D. in 1947, took the D.C.H. in 1948, and was elected M.R.C.P. in 1949. He was appointed paediatric registrar at Sheffield Children's Hospital, and senior paediatric registrar at the Liverpool Maternity Hospital in 1951. It was at this time that the illness of which he had been aware for some considerable time began to affect his working capacity and he was obliged to give up his work temporarily.

In 1955 he decided to enter general practice and was appointed to a vacancy in Liverpool. Very soon his kindliness and gentle manner endeared him to ever-increasing numbers of his patients. He threw himself heart and soul into the work of his practice, and no task was too much trouble nor any hour too late where the welfare of his patients was concerned. Thornton was most painstaking and thorough in his work, and was held in high esteem by his colleagues. The last two or three years in practice were marred by increasing disability and periods in hospital. Although he knew that his days were numbered he was never heard to complain, and even to the end retained a sharp wit and an acute sense of humour. He will be sadly missed by his patients and friends, whose sympathies go out to his widow and three children.—H. S.

A. H. WEAR, M.D., B.Hy., D.P.H.

Dr. A. H. Wear, who was medical officer of health for the Bolsover urban and the Blackwell and Clowne rural districts of Derbyshire for over thirty years, died at Crewkerne Hospital, Somerset, on April 10. He was 69 years of age.

Arthur Hyde Wear was born at Newcastle upon Tyne on November 29, 1889, the son of Dr. A. T. Wear and the nephew of Dr. Alfred Cox, formerly Secretary of the British Medical Association. From the Newcastle Royal Grammar School he entered the medical faculty of Durham University, and graduated M.B., B.S. in 1911. Three years later he obtained the degree of Bachelor of Hygiene and the Diploma in Public Health. After graduation he held the appointments of house-surgeon at Glasgow Royal Infirmary and house-physician at Newcastle Royal Infirmary. In 1913 he was appointed assistant school medical officer at Newcastle, and in 1919 assistant medical officer of health for South Shields, holding both appointments until 1923. During the whole of the first world war he served in the Royal Navy and was present at the Battle of Jutland in H.M.S. *Ajax*. In 1923 he was appointed medical officer of health for the Bolsover and Blackwell and Clowne districts, and assistant county medical officer in Derbyshire. He retired in 1956. Arthur Wear was a keen sportsman, with a special interest in golf and tennis. Of a very kindly disposition, he was respected and loved by all who knew him. He will be greatly missed by a wide circle of friends. He leaves a widow and two sons, Dr. A. R. Wear, of Wetheral, Cumberland, and Dr. L. E. Wear, of Crewkerne. —B. G. H.

Medical Notes in Parliament

BRITISH SPACE RESEARCH

The possibility of a British venture into space research, with a satellite fired from the Woomera range, is exercising the members of both Houses. Ministers have for some weeks been parrying a persistent interrogation with the assurance that such a project is under consideration, and the promise of an early statement. It is now confidently believed that the Government have reached a decision and that the announcement will be coming very soon.

The latest and firmest indication of how soon was contained in a question and answer immediately before the Commons adjourned on April 29. Mr. G. DE FREITAS (Lincoln, Lab.), who has been regularly prodding the Government, used the adjournment motion that night in an attempt by a short speech to extract more information than a long series of questions had done. The particular aspect he was concerned with was the use of the R.A.F.'s Blue Streak and Black Knight ballistic missiles as vehicles for launching into outer space satellites containing scientific instruments, and he spoke tentatively in terms of a modest project with satellites weighing about a ton and an expenditure of £10m. to £20m. He was no more successful this time than on previous occasions, the Government spokesman, Mr. W. J. TAYLOR, Parliamentary Secretary to the Ministry of Supply, making no advance from the "active consideration" line. At the end, however, Mr. DE FREITAS demanded, "Will the House have to wait days, or weeks, or months, before a decision is made?" and Mr. TAYLOR went so far as to narrow the time to days: "I hope it will not be weeks or months."

Science Fiction and the Lords

The Lords also, and by coincidence on the same day, showed their interest in the subject during their annual discussion of the Air Estimates. Their debate produced a fascinating disclosure that science fiction has invaded the House of Lords library, and that among the library's ponderous and profound volumes of leather-bound law and politics two peers had discovered another of their number immersed in a pile of brightly covered books, spellbound by adventures in space ships. This did not prevent EARL JELLICOE (who was discovered) or Lord ST. OSWALD (who was one of the discoverers) arguing strongly that Britain should enter space research as a matter of priority, and that the amount of investment in it should be not the minimum necessary to save face but the maximum the economy could stand. Both were agreed in deploring the loss of scientists and technologists to America because of the lack of a British programme—"the export of our most adventurous brains," as one of them called it. They were joined by Lord SHACKLETON with the suggestion that so costly a venture was appropriate for joint action by the Commonwealth. All these are matters which, like the use of existing military missiles for the purpose, have been at different times accepted by the Minister of Supply as matters within the scope of the Government's investigation and consideration.

THIRD READING OF MENTAL HEALTH BILL

The third reading of the Mental Health Bill on May 6 produced two important announcements by the Minister of Health. The first was that the Medical Research Council had decided to establish two new committees—one on clinical psychiatry, to advise them in this rapidly expanding field of research, of which the chairman would be Sir George Pickering, Regius Professor of Medicine at Oxford; and the other on the epidemiology of mental disorders, the purpose of which would be to provide the basis for a realistic evaluation of methods of treatment, of which the chairman would be Professor Aubrey Lewis, of the Institute of Psychiatry, Maudsley Hospital.

Role of State Institutions

The second announcement was of the Minister's intention to set up a working party, including outside experts, to examine the future role of State institutions where dangerous or violent persons are detained. (These were renamed "special hospitals" as a result of amendments to the Bill made the previous day on the report stage.) Mr. WALKER-SMITH rejected the suggestion for a departmental committee of inquiry as an inappropriate method, but agreed that it would be advantageous to think out afresh the role of the special hospitals in the mental health service and the classification of patients to be treated in them.

QUESTIONS IN THE COMMONS

Incidence of Poliomyelitis

The MINISTER OF HEALTH gave on April 29 statistics of the incidence of poliomyelitis for the past 20 years. This was asked for by Mr. S. P. VIANT (Willesden, West, Lab.). The figures given are for age 25 and over, since 1944; paralytic and non-paralytic forms were not distinguished before 1950.

Year	Final Notifications of Poliomyelitis		Deaths Due to Poliomyelitis (All Forms)
	Paralytic	Non-paralytic	
1939	Not available by age		1939 25
1940	" "	" "	1940 50
1941	" "	" "	1941 47
1942	" "	" "	1942 34
1943	" "	" "	1943 32
1944	" " 61	" "	1944 43
1945	116		1945 62
1946	101		1946 52
1947	1,258		1947 241
1948	333		1948 98
1949	890		1949 241
1950	967	328	1950 271
1951	323	204	1951 97
1952	562	180	1952 144
1953	667	268	1953 140
1954	232	91	1954 66
1955	804	370	1955 142
1956	368	218	1956 82
1957	782	238	1957 157
1958*	290	91	1958 Figures not yet available

* 1958 figures are provisional.

The MINISTER also informed Mr. VIANT that corrected notifications of poliomyelitis in England and Wales in 1958 numbered 1,993, of which 1,417 were paralytic. The number of cases which were reported among persons who had two or more injections of poliomyelitis vaccine was 178, of which 92 were paralytic.

Occurrence Shortly After Vaccination

Mr. VIANT also asked what was the number of cases of poliomyelitis in 1957 and 1958 which occurred within 30 days of vaccination, and how many of them were paralytic. Mr. WALKER-SMITH stated on May 1 that in 1957 8 and in 1958 25 cases of poliomyelitis within 30 days of a second or subsequent injection of vaccine were reported to the department. Of these, 5 and 15 respectively were paralytic. There were several reasons why poliomyelitis might occur in vaccinated persons, and it was not possible to identify the reason with certainty in an individual case. By the end of 1957 and 1958 about 1½m. and 6½m. people, respectively, had received two injections.

Army Medical Boards

The SECRETARY OF STATE FOR WAR put in perspective on April 29 the early release from service some instances of which have recently attracted considerable publicity. Answering a further series of questions on this subject, Mr. C. SOAMES stated that over the past nine years 928,000 national service men entered the Army. Medical discharges during the initial period of service—up to 16 weeks—numbered 11,000, or about 1% of the total. These figures included cases in which disability could not have been established before service. The figures showed that it was rare for discharges to result from the diverging views of medical boards, and he and the Minister of Labour had every confidence in the present system.

Mr. J. STRACHEY (Dundee, West, Lab.) and Mr. G. NABARRO (Kidderminster, Con.) pressed the contention that there was public disquiet about prominent individuals included in this very small category, and the latter suggested that there was a need for something like a tribunal of inquiry about Terry Dene, with full disclosure of the facts, including the medical reports, so that the House and the country could judge the veracity of statements made by the Army medical authorities.

Mr. SOAMES "absolutely refuted" the inferences cast on the attitude adopted by the medical authorities. There was a small proportion of men who were considered fit for service at the pre-call-up medical board but in the event were found to be unfit—1% of the total over the last nine years. The fact that the proportion was so small reflected credit on the medical profession. Occasionally it happened that one of these men was in the public eye, and that attracted publicity. He appreciated that it made feelings run high. Neither the Adjutant-General's department nor he, if he intervened, had any alternative but to discharge a man, whatever his name, if the medical advice was as definite and unequivocal as it was in the particular case.

Management in the N.H.S.

Sir KEITH JOSEPH (Leeds, North-East, Con.) asked the Minister of Health on May 4 whether he could announce the composition and terms of reference of the council he is setting up to advise on the application of modern management techniques in the National Health Service. Mr. WALKER-SMITH replied that the council would be known as the "National Health Service Advisory Council for Management Efficiency (England and Wales)," and its terms of reference were, "To advise generally on measures for improving efficiency in the National Health Service in England and Wales." The chairman will be Sir Ewart Smith.

The council would concentrate in the first instance on problems connected with the hospital service, and this was reflected in the membership. The members had been invited to serve on the council because of the personal contribution they could make as a result of their experience in the hospital service or in the promotion of management efficiency in other fields.

The members are: Mr. C. Bartlett, R.M.N., Mr. C. H. Beckett, Professor T. E. Chester, Mr. A. M. Hudson Davies, Mr. S. Hill, Dr. F. Avery Jones, Mr. S. C. Merivale, F.H.A., Mr. M. W. Perrin, F.R.I.C., Alderman R. G. Robinson, J.P., Professor Sir Arthur Thomson, Sir Edward Thompson, J.P., Mr. G. Watts, F.H.A., and Miss M. L. Young, S.R.N.

Liverpool Practice Appointment

Mrs. E. BRADDOCK (Liverpool, Exchange, Lab.) asked the Minister why he had allowed an appeal against a recent appointment to a medical practice in Liverpool; and, in view of the rule, hitherto observed throughout the Health Service, that no medical practitioner should, in the absence of special circumstances, be appointed to a vacant practice if he was already in charge of another practice which he did not undertake to abandon, whether he would make a statement on his policy in this respect. She also asked the Minister for a full statement on the terms of the recent recommendation made by the Medical Practices Selection Committee of the Liverpool Executive Council in connexion with a vacant medical practice. Mr. R. THOMPSON, Parliamentary Secretary, said the Liverpool Executive Council recommended one applicant and the Minister allowed the appeal of another, mainly because he had more adequate experience in general practice. There was no absolute rule to exclude the combination of practices. Executive councils knew that the filling of each vacancy must be considered on its merits, and the Minister saw no need to issue new instructions on this subject.

Mrs. BRADDOCK said that this had caused great consternation in the Liverpool Executive Council. It has strictly adhered in the past to the fact that one doctor should not be given another practice in the same area. Would the Parliamentary Secretary state emphatically that there was no intention of breaking the rule followed so long in the Health Service? Mr. THOMPSON: I am quite happy to give that assurance. There has been no change of emphasis or direction here.

Dr. EDITH SUMMERSKILL (Warrington, Lab.) said it was recognized that other doctors on a short list would have an opportunity to appeal after a doctor had been appointed to a vacancy, but was this very common? How often was an appellant successful? Mr. THOMPSON said he could not say without notice how often the appellant was successful, but they got quite a few cases.

Appointment of Specialists

Mr. J. CRONIN (Loughborough, Lab.) asked if the Minister would put in hand measures to enable regional hospital boards, where consultants' appointments had been terminated through no fault of their own, to re-employ these consultants in other posts without the necessity of their applying for them in competition through advertisements. Mr. WALKER-SMITH said that he was considering an amendment of the National Health Service (Appointment of Specialists) Regulations, 1950, with this point in mind.

Mr. CRONIN asked if it was not the case that under the present regime, with the advances in medical science and changes in the local population, there might be considerable necessity to redeploy consultants, and a more flexible approach was desirable. Mr. WALKER-SMITH: I think that is quite true. With the advancing and changing techniques it is desirable to try to have a flexible system.

Expenditure on Cancer Research

Mr. SYDNEY IRVING (Dartford, Lab.) asked how much money would be spent by the Minister on cancer research this year, apart from the £206,400 granted to the Institute of Cancer Research in this year's estimate. Mr. WALKER-SMITH replied that expenditure from public funds on cancer research was mainly undertaken by the Medical Research Council, who, he understood, expected to spend some £580,000 for this purpose during the current year, including the grant to the Institute of Cancer Research referred to in the question. Cancer research was also carried out in the Health Service in the course of treatment of patients, but it was impossible to make a separate estimate for the expenditure involved.

Mr. IRVING commented that the House would have nothing but praise for the effort made by voluntary bodies, but it was difficult for people to understand why in the attack on this terrible disease so much of the burden should have to fall on voluntary effort.

Vaccination Against Leprosy

Dr. STROSS asked the Secretary of State for the Colonies whether he was aware that there were prima facie grounds that vaccination by B.C.G. might prevent the incidence of leprosy; and whether he would institute a pilot scheme of vaccination in one or more of the Colonies to ascertain the value, or otherwise, of this procedure.

Mr. J. AMERY, Under-Secretary, Colonial Office, said he understood that pilot schemes of vaccination were already in progress in the Federation of Nigeria and Uganda. He was advised that it might take several years before the effectiveness could be judged.

Vital Statistics

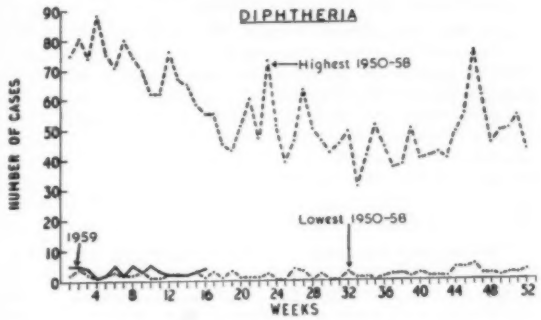
Infectious Diseases

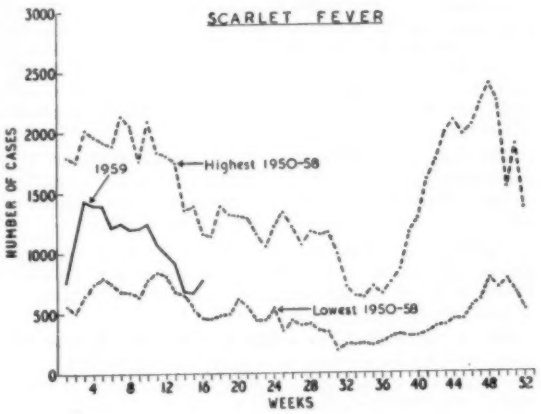
Areas where numbers of notifications were high in the latest two weeks for which figures are available:

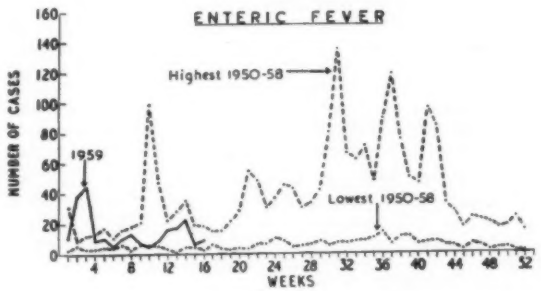
	Week Ending April 18	Week Ending April 25
Measles		
Durham	1,088	1,256
Sunderland C.B.	280	325
West Hartlepool C.B.	92	141
Gloucestershire	337	344
Bristol C.B.	141	199
Northumberland	687	708
Wallsend M.B.	92	127
Surrey	981	795
Croydon C.B.	210	197
Yorkshire West Riding	1,854	1,641
Bradford C.B.	104	110
Huddersfield C.B.	124	111
Dysentery		
Gloucestershire	19	23
Bristol C.B.	15	10
Kent	17	25
Dartford M.B.	0	15
Lancashire	97	105
Blackburn C.B.	23	36
London	115	102
Chelsea	4	22
Lewisham	4	18
Staffordshire	10	31
Newcastle-under-Lyme	0	12
Warwickshire	51	95
Coventry C.B.	24	68
Yorkshire West Riding	23	34
Kingston upon Hull C.B.	20	28
Glamorganshire	42	51
Rhondda M.B.	10	19
Typhoid Fever		
Lancashire, Preston C.B.		
Food-poisoning		
Cumberland	0	35
Cockermouth R.D.	0	34
Lancashire	24	42
Kirkby U.D.	4	18
Acute Poliomyelitis		
London	1	4
Hampshire, Southampton C.B.	2	6
Lancashire	4	4
Liverpool C.B.	2	3

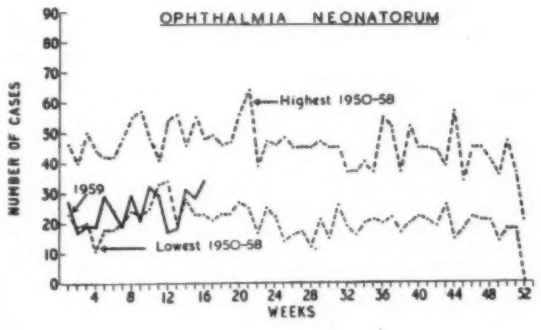
Graphs of Infectious Diseases

The graphs below show the uncorrected numbers of cases of certain diseases notified weekly in England and Wales. Highest and lowest figures reported in each week during the years 1950–8 are shown thus ------, the figures for 1959 thus ———. Except for the curves showing notifications in 1959, the graphs were prepared at the Department of Medical Statistics and Epidemiology, London School of Hygiene and Tropical Medicine.









INFECTIOUS DISEASES AND VITAL STATISTICS

Summary for British Isles for week ending **April 25** (No. 16) and corresponding week 1958.

Figures of *cases* are for the countries shown and London administrative county. Figures of *deaths* and *births* are for the whole of England and Wales (London included), London administrative county, the 17 principal towns in Scotland, the 10 principal towns in Northern Ireland, and the 14 principal towns in Eire.

A blank space denotes disease not notifiable or no return available.

The table is based on information supplied by the Registrars-General of England and Wales, Scotland, N. Ireland, and Eire, the Ministry of Health and Local Government of N. Ireland, and the Department of Health of Eire.

CASES	1959					1958				
	Eng. & Wales	Lond.	Scot.	N. Ire.	Eire	Eng. & Wales	Lond.	Scot.	N. Ire.	Eire
Diphtheria ..	4	1	5	0	2	1	0	4	0	1
Dysentery ..	837	102	152	8	3	1,010	95	171	12	6
Encephalitis, acute	1	0		0		5	0		0	
Enteric fever:										
Typhoid ..	5	0	0	0	1	3	1	0	0	2
Paratyphoid ..	4	0	1 (B)	0		4	2	0	0	4 (B)
Food-poisoning ..	283	85	12	0		127	25	10	0	
Infective enteritis or diarrhoea under 2 years				8	18				9	29
Measles*	14,474	695	642	331	236	5,057	444	153	46	12
Meningococcal infection	23	3	10	1	1	33	3	9	0	5
Ophthalmia neonatorum	34	0	6	0		23	7	6	0	
Pneumonia† ..	340	24	197	13	6	556	41	269	13	5
Poliomyelitis, acute:										
Paralytic ..	10	3	1	1	2	15	2	2	3	3
Non-paralytic ..	11	1	1			4	0			
Puerperal fever§ ..	223	37	11	0		173	27	13	3	
Scarlet fever ..	769	37	53	31	23	599	37	61	32	21
Tuberculosis:										
Respiratory ..	562	59	78	9		559	56	142	25	
Non-respiratory	72	7	9	3		62	4	21	5	
Whooping-cough ..	710	12	64	44	158	539	21	54	13	11

DEATHS	1959					1958				
	Eng. & Wales	Lond.	Scot.	N. Ire.	Eire	Eng. & Wales	Lond.	Scot.	N. Ire.	Eire
Diphtheria ..	0	0	0	0	0	0	0	0	0	1
Dysentery ..	0	0		0		0	0		0	
Encephalitis, acute		0			0		0			0
Enteric fever ..	0	0	0	0		1	0	0	0	
Infective enteritis or diarrhoea under 2 years	6	0	1	0	1	5	0	0	0	2
Influenza	58	1	0	4	8	44	1	2	1	2
Measles		0	0	0	0		1	0	0	0
Meningococcal infection		0	1				0	0		
Pneumonia ..	492	38	30	25	19	696	54	34	13	10
Poliomyelitis, acute	1	0		0	0	5	1		1	0
Scarlet fever ..		0	0	0	0		0	0	0	0
Tuberculosis:										
Respiratory ..	78	6	5	2	2	130	9	11	0	2
Non-respiratory		0	2	0	0		2	2	0	2
Whooping-cough	0	0	0	1	0	0	0	0	0	0
Deaths 0–1 year ..	331	36	35	7	14	356	41	34	6	21
Deaths (excluding stillbirths) ..	9,487	703	593	153	183	11,465	878	708	136	235
LIVE BIRTHS ..	14,815	1280	1100	311	420	15,382	1273	1005	292	435
STILLBIRTHS ..	360	26	27			361	34	26		

* Measles not notifiable in Scotland, whence returns are approximate.
† Includes primary and influenzal pneumonia.
§ Includes puerperal pyrexia.

Medical News

University of Bristol Jubilee.—The fiftieth anniversary of the granting of the royal charter of Bristol University by King Edward VII on May 24, 1909, will be celebrated at the end of May. At a special Congregation on May 26 an honorary doctorate of medicine will be conferred on Professor ROBERT PLATT, professor of medicine at the University of Manchester.

F.R.C.P. and M.R.C.P.—At the quarterly comitia of the Royal College of Physicians of London, held on April 30, the following were elected Fellows of the College:

Dr. Min Sein (Burma); Dr. E. F. Brooks (Canada); Dr. R. Kasliwal (India); Dr. C. B. Prowse (Hove); Dr. I. O. Thorburn (Australia); Dr. A. Landau (South Africa); Dr. F. J. Wright (Edinburgh); Dr. A. L. Winner (London); Dr. M. Williams, (New Zealand); Dr. A. L. Jacobs (London); Dr. W. H. P. Hill (Canada); Dr. W. H. P. Cant (Birmingham); Dr. N. M. Jacoby (Tunbridge Wells); Dr. C. A. Lillicrap (Lincoln); Dr. P. E. C. Manson-Bahr (Kenya); Dr. N. H. Martin (London); Dr. J. W. Paulley (Ipswich); Dr. G. S. Graveson (Winchester); Dr. J. Apley (Bath); Dr. T. C. Studdert (Carlisle); Dr. L. P. R. Fourman (Cardiff); Dr. G. O. Richardson (Newcastle upon Tyne); Dr. M. J. Parsonage (Leeds); Dr. J. R. Bolton (Bath); Dr. J. J. Kempton (Reading); Dr. G. C. Wells (London); Dr. R. R. Andrews (Australia); Lieutenant-Colonel J. P. Baird, R.A.M.C. (Singapore); Dr. W. St. Clair Symmers (London); Dr. J. N. M. Chalmers (Birmingham); Dr. E. G. Wade (Manchester); Dr. H. W. Balme (London); Dr. E. Kelly (London); Dr. J. Badenoch (Oxford); Dr. A. C. Boyle (London); Dr. P. Hugh-Jones (London); Professor E. Stengel (Sheffield); Professor H. Barcroft, F.R.S. (London); Dr. J. D. W. Pearce (London); Dr. G. D. W. Cameron (Canada); Dr. R. R. Race, F.R.S. (London); Professor Wilson Smith, F.R.S. (London).

The following, having satisfied the censors' board, were elected Members of the College:

Drs. A. S. Alvarez, J. G. Banwell, R. W. A. C. Barton, D. Basu, A. D. Cameron, B. G. B. Christie, A. N. G. Clark, D. N. Croft, M. J. R. Dawkins, M. A. Denborough, J. M. Evans, A. G. Giddins, H. Gordon, E. L. Harris, A. B. Herring, K. P. Jain, G. B. Kiddle, R. K. Levick, D. A. Lillicrap, I. Macalpine, C. F. McCarthy, A. W. McKenzie, A. C. Markus, E. Moran, G. Preswick, D. Rabinowitz, M. D. Rawson, A. R. Ridley, B. H. B. Robinson, D. C. Robinson, S. J. Saunders, H. S. Schutta, B. A. Scobie, M. C. Sidey, A. J. Smith, C. M. Tonks, I. Weinbren, L. G. Whitby, M. J. Williams, G. E. W. Wolstenholme, B. Woods, N. L. Wright, H. J. Wyatt, D. N. Wysham.

Royal Faculty of Physicians and Surgeons, Glasgow.—At a meeting of the Faculty on April 6, the following were admitted fellows of Faculty:

Qua Physician.—W. Chan, J. S. Eapen, W. Hamilton, J. D. Kinloch, J. K. G. Macarthur, P. D. Moylan, N. K. Sinha. *Qua Surgeon.*—S. Alexander, J. P. Galloway, S. Gopala-Pillai, S. Rao, C. R. Subramaniam, J. R. Thomson.

Social Workers.—The Working Party on Social Workers in the Local Authority Health and Welfare Services, whose report was issued last week (H.M.S.O., London. Price 15s. net), foresees a greatly increased demand for social workers, particularly in connexion with mental health and the care of handicapped persons. The report recommends a new course of training for social workers leading to a national qualification. In addition to the main body of social workers who have had this general training, there will be a need for professionally trained and experienced social workers—such as psychiatric social workers, almoners, and family caseworkers—to undertake the investigation of problems of special difficulty, and also for "welfare assistants," who will have had a short but systematically planned in-service training. The working party, of which Miss E. L. Younghusband was the chairman, estimates that over the next 10 years about 5,500 whole-time officers with the new general training will be needed—an increase of 75% over the present number. The working party also recommends a substantial increase in the number of professionally trained social workers and the recruitment of at least 200 welfare assistants annually for five years. The report emphasizes the need for close liaison between social workers and their colleagues in related services, such as health visitors, home nurses, doctors, children's officers, and many others.

Royal Air Force.—Mr. F. J. G. JEFFERIS, deputy director of the V.D. clinic at St. Mary's, has been appointed honorary civil consultant in venereology, and Mr. J. P. MONKHOUSE, E.N.T. surgeon at the Middlesex Hospital, honorary civil consultant in otology.

American Monograph Prizes.—The American Academy of Arts and Sciences is to award an annual $1,000 prize "to the author of an especially meritorious unpublished monograph in the physical and biological sciences," a category which is to include medicine. To be eligible for an award in any year, a manuscript must be received by the Academy before October 1 of that year. Details may be obtained from the Committee on Monograph Prizes, American Academy of Arts and Sciences, 280 Newton Street, Brookline Station, Boston 46, Massachusetts, U.S.A.

"World-wide Abstracts."—This is a monthly abstracting journal intended for the general practitioner. It is published by the Excerpta Medica Foundation "and distributed as a service to physicians by Warner-Chilcott Laboratories." The editors are Dr. MORRIS FISHBEIN (Chicago) and Dr. MARTINUS W. WOERDEMAN. In addition to abstracts, each issue of *World-wide Abstracts* contains a review of some subject of major concern to practitioners. Inquiries to Excerpta Medica Foundation, New York Academy of Medicine Building, 2, East 103 Street, New York, 29.

University of Edinburgh.—The University Court has appointed Professor ERIC C. MEKIE as director of studies to the Edinburgh Postgraduate Board for Medicine from October 1. He succeeds Sir ALEXANDER G. BIGGAM.

University of Aberdeen.—On July 10 the University will confer an honorary Doctorate of Laws on Emeritus Professor E. W. H. CRUICKSHANK, professor of physiology at the University from 1936 to 1958.

Mr. A. H. Barber, the Oldham gynaecologist, was not short-listed by the advisory committee considering candidates for a consultant appointment with the Ashton-under-Lyne, Hyde, and Glossop Group of Hospitals (*The Times,* May 7). This is the second such post for which Mr. Barber has applied unsuccessfully (see *Journal,* May 9, p. 1253). As a result, the Oldham and District Hospital Management Committee decided unanimously on May 6 to ask the Minister of Health to hold an inquiry into the proceedings of the advisory committee. It is now learned (*Manchester Guardian,* May 8) that the Minister has asked the secretary of the Manchester Regional Hospital Board for a full report.

Dr. G. P. McNicol has been awarded a Harkness Fellowship of the Commonwealth Fund for 1959, tenable for one or two years in the United States. He is assistant in the department of Maternal Medicine and Therapy, University of Glasgow, and medical registrar, Stobhill Hospital, Glasgow.

Sir Wilfred Fish, president of the General Dental Council and honorary director of the Department of Dental Science of the Royal College of Surgeons of England, will have the honorary degree of Doctor of Dental Science, Durham University, conferred upon him on July 3.

Dr. D. A. Long has been appointed chief medical adviser and head of the medical research department of the Wellcome Foundation Limited.

Dr. Long had been a member of the staff of the Medical Research Council at the National Institute for Medical Research since 1948. He held previous appointments at St. Bartholomew's Hospital Medical School and at the London School of Hygiene and Tropical Medicine. In 1957-8 Dr. Long was visiting professor in microbiology in the School of Medicine at the University of Pittsburg, U.S.A.

COMING EVENTS

Institute of Dermatology.—Semi-permanent exhibition available till May 25 by Dr. J. A. DUDGEON on "Virus Diseases."

Symposium on "The Staphylococcus."—This symposium for consultant pathologists will be held at the Postgraduate Medical School of London, Ducane Road, London, W.12, from July 15 to 17. Applications by June 17. Details from the Dean, Postgraduate Medical School. See also advertisement p. 60 of this week's *Journal*.

Dental and Medical Society for the Study of Hypnosis.—"The Theory and Practice of Hypnosis" will be the subject of a week-end study group to be held in Manchester on June 6 and 7. Applications from medical practitioners to Dr. J. R. JAFFE, "Windover," 23, Sheepfoot Lane, Prestwich, Manchester.

Multiple Sclerosis Society.—The annual general meeting will take place at the Livingstone Hall, Broadway, Westminster, London, S.W.1, on June 17 at 6 p.m.

The following is a list of medical meetings taking place immediately preceding or during the period of the Joint B.M.A./C.M.A. Annual Meeting in Edinburgh. An asterisk indicates that guests should be introduced by a member.

British Tuberculosis Association.—Annual meeting to be held in Cambridge from July 1 to 4. Details from the Secretary, 59, Portland Place, London, W.1.

Oxford Ophthalmological Congress.—To be held in Oxford from July 1 to 4. Details from Mr. I. FRASER, 21, Dogpole, Shrewsbury.

***Society of Endocrinology.**—The Ordinary Meeting will be held at Cambridge on July 9. Details from Dr. C. R. AUSTIN, National Institute for Medical Research, Mill Hill, London, N.W.7.

British Association of Dermatology.—Annual meeting to be held in Glasgow from July 9 to 11. Details from Dr. H. J. WALLACE, Honorary Secretary, Institute of Dermatology, St. John's Hospital for Diseases of the Skin, Lisle Street, London, W.C.2.

***Pathological Society of Great Britain.**—Meeting to be held in Cardiff from July 9 to 11. Details from Professor W. DOWNIE, Department of Bacteriology, The University, Liverpool.

***The Thoracic Society.**—Summer meeting to be held in Oxford on July 10 and 11. Details from Dr. K. ROBSON, 72, Harley House, London, N.W.1.

International Congress of the British Association of Plastic Surgeons.—This congress will be held in London from July 12 to 17. Details from Mr. D. MATTHEWS, Organizing Secretary, International Congress on Plastic Surgery, c/o Institute of Child Health, Hospital for Sick Children, Great Ormond Street, London, W.C.1.

Association of Industrial Medical Officers.—Annual provincial meeting to be held in Glasgow from July 13 to 17. Details from Dr. T. S. WILSON, Honorary Secretary, Scottish Group of Association of Industrial Medical Officers, 23, Montrose Street, Glasgow, C.1.

British Congress of Obstetrics and Gynaecology.—To be held in Cardiff from July 14 to 16. Details from Professor A. S. DUNCAN, Department of Obstetrics and Gynaecology, The Maternity Hospital, Glossop Terrace, Cardiff.

***Royal Medico-Psychological Association.**—Annual meeting to be held in Glasgow from July 15 to 18. Details from the General Secretary, 11, Chandos Street, London, W.1.

***British Association of Urological Surgeons.**—The combined meeting with the Canadian Urological Association will be held in Glasgow from July 15 to 18. Details from the Association, 47, Lincoln's Inn Fields, London, W.C.2.

SOCIETIES AND LECTURES

A fee is charged or a ticket is required for attending lectures marked ●. Application should be made first to the institution concerned.

Tuesday, May 19

DUBLIN UNIVERSITY: SCHOOL OF PHYSIC, TRINITY COLLEGE.—At Anatomy Theatre, 4.30 p.m., John Mallet Purser Lecture by Professor R. J. V. Pulvertaft: Lymphocyte in Malignant Disease (illustrated by a film).

INSTITUTE OF DERMATOLOGY.—At British Institute of Radiology, 5 p.m., Dr. P. Wade: Radiotherapy of Malignant Skin Conditions (I).

●INSTITUTE OF OBSTETRICS AND GYNAECOLOGY.—At Chelsea Hospital for Women, 4.30 p.m., Miss J. Barnes: Practical Aspects of Pelvic Endometriosis.

ST. MARY'S HOSPITAL MEDICAL SCHOOL.—At Wright-Fleming Theatre, 5 p.m., Dr. Charles Pinckney: Care of the Premature Baby.

WEST END HOSPITAL FOR NEUROLOGY AND NEUROSURGERY.—5.30 p.m., Dr. G. A. D. Gordon: Ultra-sonic Rays in Neurosurgery.

Wednesday, May 20

INSTITUTE OF DERMATOLOGY.—5.30 p.m., Dr. H. Haber: Eosinophilic Granuloma of the Skin.

INSTITUTE OF DISEASES OF THE CHEST.—5 p.m., Dr. R. S. F. Schilling: Recent Studies of Chronic Respiratory Disease in Cotton Workers.

LEEDS UNIVERSITY.—At Littlewood Hall, General Infirmary at Leeds, 5.15 p.m., Dr. Peter Miescher (Basle): Pathogenesis of Lupus Erythematosus.

LONDON AMATEUR BOXING ASSOCIATION.—At British Railways Film Unit Office, 25, Saville Row, W., 8 p.m., agenda includes film on sporting Injuries.

POSTGRADUATE MEDICAL SCHOOL OF LONDON.—2 p.m., Dr. B. W. Lacey: Environment and Microbial Antigens.

WILLESDEN GENERAL HOSPITAL MEDICAL SOCIETY.—At Department of Physical Medicine, Willesden General Hospital, 8.45 p.m., Dr. W. Howlett Kelleher: Poliomyelitis.

Thursday, May 21

HONEYMAN GILLESPIE LECTURE.—At Anatomy Theatre, University New Buildings, Edinburgh, 5 p.m., Dr. M. B. Matthews: Some Observations on the Aetiology of Aortic Stenosis.

NUFFIELD ORTHOPAEDIC CENTRE.—At Wingfield-Morris Orthopaedic Hospital, 8.30 p.m., Professor J. Trueta: Reassessment of the Problem of Osteochondritis of the Hip.

POSTGRADUATE MEDICAL SCHOOL OF LONDON.—4 p.m., Professor W. J. Butterfield: Oral Preparations in the Treatment of Diabetes.

ROYAL SOCIETY OF TROPICAL MEDICINE AND HYGIENE.—At 26, Portland Place, London, W., 7.30 p.m., Dr. Ivan Polunin: Muruts of North Borneo and their Declining Population. A discussion will follow.

WEST LONDON MEDICO-CHIRURGICAL SOCIETY.—5.45 p.m., visit to Chiswick works of London Transport Board.

Friday, May 22

BIOCHEMICAL SOCIETY.—At National Institute for Research in Dairying (University of Reading), Shinfield, Berks, 383rd meeting.

●INSTITUTE OF DERMATOLOGY.—5.30 p.m., clinical demonstration by Dr. H. J. Wallace.

POSTGRADUATE MEDICAL SCHOOL OF LONDON.—10 a.m., Mr. Clifford Jones: Vasomotor Disturbances of the Hands.

ROYAL COLLEGE OF SURGEONS OF ENGLAND.—5 p.m., Charles Tomes Lecture by Lord Cohen of Birkenhead: Facial Neuralgia.

INSTITUTE OF LARYNGOLOGY AND OTOLOGY.—5.30 p.m., clinical lecture by Mr. Maxwell Ellis: The Theory of Voice Production.

Saturday, May 23

CAMBRIDGE UNIVERSITY MEDICAL SCHOOL.—Symposium on Gastro-intestinal Diseases at Addenbrooke's Hospital. Speakers, 10.30 a.m., Dr. A. P. Dick, Indigestion; 11.15 a.m., Dr. J. M. Walshe, Some Views on Treatment of Liver Disease; 12 noon, Dr. M. J. Grayson, clinical aspects, and Dr. F. R. Berridge, radiological aspects of Anaemia in Gastro-intestinal Diseases; 2 p.m., demonstration of clinical cases and methods of investigation in gastro-enterology; 3.15 p.m., Dr. Berridge, Cineradiography in Diseases of the Oesophagus; 3.45 p.m., Mr. B. McN. Truscott, The New Look in Pancreatic Surgery.

BIRTHS, MARRIAGES, AND DEATHS

BIRTHS

Kelsall.—On May 2, 1959, in London, to Margaret (formerly Miller), wife of Dr. A. R. Kelsall, a daughter.

MARRIAGES

White—Mumford.—On April 6, 1959, in the Memorial Chapel, Glasgow University, Egerton Carl White, T.D., M.B., Ch.B., to Maisie Dora Mumford (formerly Swinn).

DEATHS

Archdeacon.—On April 22, 1959, Timothy Archdeacon, L.R.C.P.&S.Ed., L.R.F.P.S., of Pulborough, Sussex.

Joseph.—On April 18, 1959, at 8, Ormonde Road, Branksome Park, Bournemouth, Hants, Mampilly Antony Joseph, M.B., B.S., formerly of "Malibar," Station Road, Pendlebury, Manchester.

Mackay.—On April 12, 1959, at Ellesmere, Salop, William Robert Hope Mackay, M.D., of The Hill, Ellesmere.

Smerdon.—On April 6, 1959, at Cliftonville, Edgar Wilmot Smerdon, M.D., F.R.C.S., late of 81, Watcombe Road, Southbourne, Bournemouth, Hants, formerly of Dorchester, Dorset, and Wenchow, China.

Stableford.—On April 16, 1959, at 28, Magazine Brow, Wallasey, Cheshire, Frank Barney Gorton Stableford, M.R.C.S., L.R.C.P.

Thornton.—On April 13, 1959, at 201, Edge Lane, Liverpool, Kenneth Bruce Thornton, M.D., M.R.C.P., D.A., D.C.H.

Travers.—On April 13, 1959, in Linton Hospital, near Maidstone, Kent, Frederick Thomas Travers, O.B.E., M.B., F.R.C.S.Ed., J.P., of Park View, Maidstone, aged 89.

Wear.—On April 10, 1959, at Crewkerne Hospital, Som, Arthur Hyde Wear, M.D., D.P.H., B.Hy., late of Mansfield, Notts, aged 69.

Whitamore.—On April 9, 1959, at his home, the Old Rectory, Thorne, near Yeovil, Somerset, Vernon Northwood Whitamore, O.B.E., F.R.C.S.Ed., Lieutenant-Colonel, I.M.S. (retired), aged 79.

Any Questions?

We publish below a selection of those questions and answers which seem of general interest. It is regretted that it is not possible to supply answers to all questions submitted.

The 40-mm. Test

Q.—*What is the technique of the test used in the R.A.F. in which the subject blows up a column of mercury and keeps it up by exhalation, and what information does the test provide?*

A.—The test is described in *The Medical Examination of Civilian Aviators*[1] as follows. "With the nose clipped the candidate is asked to empty the lungs completely, inhale fully, blow the mercury to the height of 40 mm. and maintain it there without breathing as long as possible, the pulse being counted in periods of five seconds during the performance of the test. The average time in a large number of cases tested is between 50 and 60 seconds. A time less than 40 seconds is very unsatisfactory. In a good subject the pulse rate may remain practically unaffected, or may rise gradually in rate from 73 to 96, according to the time the breath is held. The pulse may rise almost at once from 72 to 84 or 96, and be sustained there. A large rise in rate—for example, from 72 to 132 or 144—is unsatisfactory.

"The test is to be recorded thus: First, the number of seconds during which the mercury column is sustained, then the normal sitting pulse rate per five seconds taken before beginning the test, and then the number of pulsations in each five-second period, the time taken to blow the mercury to 40 mm. being ignored. The normal sitting rate should be separated by a stroke from the first figure of the pulse response during the test—for example, 50 seconds 6/6677789888. This test affords information as to the stability of the nervous centres controlling respiration and circulation, and of the power and endurance of the subject."

It is not now generally considered that the test has any value in assessing the respiratory and circulatory reserves of normal men. The pattern of the changes in pulse rate is variable, but only gross abnormalities can be detected in this way. It is also doubtful whether the test of endurance is of any significance, apart from the apprehension produced in the subject by the prospect of having to perform it. The 40-mm. test is no longer used in the Royal Air Force.

REFERENCE

1 *The Medical Examination of Civilian Aviators*, 1928. C.A. Publication No. 1, ed. 2. Air Ministry, London.

Quality of Semen

Q.—*What treatment would benefit fertility in a man with the following semen analysis: amount, 2.5 ml.; reaction pH, 8.0; count, 3,500,000 per ml.; motility good, but only an occasional motile form seen?*

A.—Before any opinion can be expressed on prognosis or treatment the seminal analysis should be repeated twice. Marked variability in the semen is sometimes encountered and a single bad specimen may have no special significance. However, if repeated analyses produce the same result, then without doubt the prognosis is poor although not entirely hopeless. One needs to know more about the patient before advice on treatment can be given. For example, is there a varicocele? If so, its surgical cure might lead to a great seminal improvement. Are the testicles of normal size or are they small and flabby? Unless there is associated eunuchoidism, small flabby testicles would give a very poor prognosis. Is there a history of epididymo-orchitis, heavy smoking, or alcoholic intake? Any of these might affect the prognosis and influence the choice of treatment.

Apart from general simple measures, such as the wearing of loose-fitting underpants, a trial of cold-water sponging of the testicles morning and night, and eliminating excessive tobacco and alcohol consumption, it is not possible to give specific advice on treatment. Certainly hormone treatment is likely to prove disappointing. If there is eunuchoidism treatment with gonadotrophins may be useful, otherwise it will not. Artificial insemination of defective semen such as this is very unlikely to lead to conception. Centrifugation of the semen in order to concentrate the spermatozoa has been advocated, but in the writer's opinion is unlikely to help.

Steroids in Migraine

Q.—*What is the rationale of giving steroids in attacks of migraine?*

A.—There is no simple answer to this question, any more than there would be to one about the rationale for giving steroids in rheumatoid arthritis. One may say, however, that allergy may play a part in initiating a migraine attack in certain instances and prednisone, prednisolone, *et hoc genus omne* are highly effective remedies for allergy. Other "anti-allergic" drugs, such as the antihistaminics, may be useful in nausea, and certainly in migraine one of the important uses of prednisone, etc., is in preventing nausea due to ergotamine. But it has been claimed on high authority[1] that, given early in an attack, corticoids may prevent its development. Unless allergy be the cause, it is difficult to explain its effect.

REFERENCE

1 Graham, J. R., *Treatment of Migraine*, 1956. Churchill, London.

Vaccination in Children with Cranial Injury

Q.—*Is smallpox vaccination contraindicated in a child suffering from convulsions after a birth injury? Is there any increase in the incidence of post-vaccinial encephalitis in such cases?*

A.—There are no reliable figures available on the incidence of post-vaccinial encephalitis in children suffering from convulsions after a birth injury. Such information would be extremely difficult both to collect and to assess, but on general principles it is advisable to use immunizing agents cautiously in such cases, particularly when there is a risk of neurological sequelae associated with the vaccine. In this country, where the risk of contracting smallpox is slight, it would be advisable to postpone Jennerian vaccination until a later age.

Correction.—In the article on coronary artery disease by M. F. Oliver, part I (April 25, page 1107), glyceryl trinitrate is said to be dispensed in a chocolate base unless otherwise specified. The *B.P.* specification is now a mannitol base. In part II of the article (May 2, page 1176) noradrenaline is said to be given by intravenous infusion of isotonic saline. This should have been isotonic glucose.

Collected Articles from the "British Medical Journal"

The following books are available through booksellers or from the Publishing Manager, B.M.A. House. Prices, which include postage, are now the same for both inland and overseas.

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Refresher Course for General Practitioners, Volumes 2 and 3 (26s. 9d. each).

Clinical Pathology in General Practice (22s. 3d.).

Any Questions?, Volumes 2 and 3 (8s. 3d. each).

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